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Glazener CMA, Evans JHC

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[Intervention Review]

Desmopressin for nocturnal enuresis in children

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ABSTRACT

Background

Enuresis (bed-wetting) is a socially disruptive and stressful condition which affects from 15% to 20% of five year olds, and up to 2% of young adults.

Objectives

To assess the effects of desmopressin on nocturnal enuresis in children, and to compare desmopressin with other interventions.

Search methods

We searched the Cochrane Incontinence Group Specialised Trials Register (searched 10 May 2006). The reference list of the original version of this review was also searched.

Selection criteria

All randomised controlled trials of desmopressin for nocturnal enuresis in children were included in the review. Trials focused solely on daytime wetting were excluded.

Data collection and analysis

Two reviewers independently assessed the quality of the eligible trials and extracted data.

Main results

Forty seven randomised controlled trials involving 3448 children (of whom 2210 received desmopressin) met the inclusion criteria. The quality of many of the trials was poor.

Desmopressin was effective in reducing bed-wetting during treatment, compared with placebo (e.g. 20 µg: 1.34 fewer wet nights per week; 95% confidence interval (CI) 1.11 to 1.57), and children were more likely to become dry (e.g. 118/146, 81% versus 140/142, 98% still wet; relative risk (RR) for failure to achieve 14 dry nights with 20 µg was 0.84; 95% CI 0.79 to 0.91). However, there was no difference between the two patient groups after treatment was finished. There was no clear dose-related effect of desmopressin, but the evidence was limited. Data which compared oral and nasal administration were too few to be conclusive.

In four small trials, there were no significant differences between desmopressin and alarms during treatment when these were used separately, but the chance of failure or relapse after treatment stopped was lower after an alarm in two small trials (40/62, 65% versus 26/57, 46%; RR 1.42, 95% CI 1.05 to 1.91).

Although children had fewer wet nights during treatment when they used desmopressin combined with alarm treatment compared with alarms alone (WMD -0.83, 95% CI -1.11 to -0.55), there were no significant differences either in failure rates during treatment (RR 0.88; 95% CI 0.73 to 1.05) or for relapse after treatment stopped (105/213, 49% versus 118/214, 55%: RR 0.91, 95% CI 0.76 to 1.08).

Comparison with some tricyclic drugs (e.g. amitriptyline) suggested that they might be as effective as desmopressin, although in two trials children were less likely to achieve 14 dry nights with imipramine than desmopressin (RR 0.44, 95% CI 0.27 to 0.73) but there was not enough information about subsequent relapse. There were more side effects with the tricyclics. Desmopressin may be better than diclofenac or indomethacin.

There was not enough information to evaluate the relative effects of behavioural or complementary treatments against desmopressin.

Authors' conclusions

Desmopressin rapidly reduced the number of wet nights per week experienced by children, but the limited evidence available suggested that this was not sustained after treatment stopped. Comparison with alternative treatments suggested that desmopressin and tricyclics had similar clinical effects during treatment, but that alarms may produce more sustained benefits. However, based on the available limited evidence, these conclusions are only tentative. Children should be advised not to drink more than 240 ml (8 ounces) of fluid during the evening before desmopressin treatment in order to avoid the possible risk of water intoxication.

PLAIN LANGUAGE SUMMARY

Desmopressin for bedwetting in children

Bedwetting is a distressing and stressful condition for children and their families. Some children take longer than others to stop bedwetting. Up to 20% still wet at the age of five years, but by the age of 16 only 2% or less do so. Desmopressin is a drug which reduces bedwetting by reducing the amount of urine produced at night. It is taken before bedtime, and the children are also advised not to drink more than 240 ml (8 ounces) of fluid in the evening. However, it only works on the nights when it is used, so does not cure the problem in the long term.

When desmopressin is used, most of the children have fewer wet nights (one night less on average per week) and more become dry (19% compared with only 2% using dummy treatment in five trials involving 288 children). However, many children start wetting again when treatment stops. On the other hand, more children remain dry when alarm treatment is finished (54% after alarm compared with 35% after desmopressin in two trials involving 119 children). Adding desmopressin to alarm treatment did not result in better cure rates after the end of treatment (51% remained dry after combination treatment compared with 45% after alarm alone).

Those using desmopressin (or their parents) should be warned that over-drinking before bedtime should be avoided as this may lead to serious, but rare, adverse effects. Drugs called tricyclic antidepressants have a similar effect to desmopressin and are cheaper, but have more adverse effects. There are few adverse effects with alarms, other than short-term disruption for the family. In summary, alarms take longer to reduce bed-wetting, but their effect may persist longer than desmopressin.

BACKGROUND

This is one of seven reviews of interventions for bed-wetting, or non-organic nocturnal enuresis. The others focus on: tricyclics and related drugs (Glazener 2004e); other drugs (Glazener 2004c); alarms (Glazener 2004a); simple behavioural interventions (Glazener 2004d); complex behavioural interventions (Glazener 2004b); and miscellaneous and complementary therapy (in preparation). All seven reviews were based on the work of Lister-Sharp and her colleagues at the Centre for Reviews and Dissemination at the University of York, United Kingdom (Lister-Sharp 1997).

Nocturnal enuresis is the involuntary loss of urine at night, in the absence of organic disease, at an age when a child could reasonably be expected to be dry (by consensus, at a developmental age of five years) (APA 1980; WHO 1992). Although bed-wetting is pathologically benign and has a high rate of spontaneous remission, it may bring social and emotional stigma, stress and inconvenience to both the children with enuresis and their families (Fitzwater 1992). Children who wet the bed may experience parental disapproval, sibling teasing and repeated treatment failure, which may lower self-esteem (Warzak 1993). The children may also be at increased risk of emotional and physical abuse (Warzak 1993). Consequently, it is important that enuresis is properly managed on 'humane grounds' (Moffatt 1994).

Although daytime wetting is a significant problem, and is often associated with bed-wetting, it is usually considered separately. It has been suggested that there are different aetiologies underlying the two conditions (Jarvelin 1989). If daytime symptoms are present, investigations to identify physical causes such as urinary tract dysfunction, congenital malformation and neurogenic disorders are usually necessary (Djurhuus 1992). An organic cause is more often found in children with daytime wetting: more structural abnormalities and functional disorders of the urinary tract were found in daytime wetters than controls (Jarvelin 1990).

Prevalence and causes

Nocturnal enuresis is a complaint that affects many families. Estimating the prevalence of nocturnal enuresis is difficult, however, because there is variation in methods of diagnosis and definitions (de Jonge 1973; Krantz 1994). In the United Kingdom, the generally quoted prevalence rates are that 15% to 20% of five year olds, 7% of seven year olds, 5% of ten year olds, 2% to 3% of 12 to 14 year olds and 1% to 2% of those aged 15 and over wet the bed twice a week on average (Blackwell 1989; Rutter 1973). The incidence of nocturnal enuresis is particularly high amongst children in residential care (Morgan 1970). About 1% of adults remain enuretic. Without treatment, about 15% of bed-wetting children become dry each year (Forsythe 1974).

The causes of nocturnal enuresis are unclear (Lister-Sharp 1997). Genetic (APA 1980 1980; Bakwin 1971; Bakwin 1973; Eiberg 1995), physiological (Djurhuus 1992; Norgaard 1993) and psychological (Devlin 1991; Moffatt 1989; Rutter 1973; Shaffer 1977) factors, as well as delay in maturation of the mechanism for bladder control (Jarvelin 1989; Koff 1995), have been suggested. Other factors which may contribute to bed-wetting include: constipation, sleep apnoea, upper airway obstructive symptoms (Maizels 1993), diet and intake of mild caffeine drinks with diuretic effects (e.g. cola) (Blackwell 1989).

Interventions

Pharmacological, psychological/behavioural and a variety of 'unconventional' interventions are commonly used for people who wet the bed.

Pharmacological interventions include desmopressin, tricyclic drugs (amitriptyline, dothiepin, doxepin, trimipramine, clomipramine, desipramine, imipramine, lofepramine, nortriptyline and protriptyline) (Glazener 2004e); drugs related to the tricyclics (viloxazine, desipramine, mianserin and maprotiline) (Glazener 2004e); and amphetamine, diazepam and oxybutynin (Glazener 2004c). However, some of these drugs are now contraindicated. Simple behavioural interventions include reward systems (such as star charts), lifting, scheduled wakening (Glazener 2004d), and alarms and over-learning (after successful alarm treatment) (Glazener 2004a). Complex behavioural interventions include multidimensional behavioural treatment such as dry bed training or full spectrum home training (Glazener 2004b). Less common interventions include: psychotherapy, retention control training, surgery, fluid deprivation and complementary therapies.

This review is restricted to pharmacological treatment with desmopressin, or to any other intervention that is compared with, or used in combination with, desmopressin.

Desmopressin

Desmopressin is an analogue of the human pituitary hormone arginine vasopressin. Its antidiuretic effect results from increased reabsorption of water from the kidney, leading to a reduced volume of more concentrated urine entering the bladder (Djurhuus 1992). In 1972, desmopressin was introduced in a dropper bottle allowing drops to be placed into the nose. It has also become available as a measured dose spray giving doses in multiples of 10 µg; a single dose pipette giving doses in multiples of 20 µg; and 0.2 mg oral tablets. Generally, 20 µg to 40 µg is given intranasally at bedtime irrespective of age and body weight (Harris 1989). Although initially prescribed for short-term treatment, longer-term treatment may be considered appropriate for some children. It has been recommended that after three months, treatment should be withdrawn for at least one week pending reassessment (BNF 2002).

About 10% of intranasal desmopressin is absorbed from the nasal mucosa. The maximum plasma concentration of desmopressin is reached within an hour, and the biological effect lasts for 10 to 12 hours (Harris 1989).

A review of the adverse effects of desmopressin for nocturnal enuresis noted that 22 adverse experiences, most commonly nasal irritation and nose bleeds, were reported in seven published studies (Hjalmas 1993). Twelve additional published studies reported no adverse effects. Although 21 cases of water intoxication were spontaneously reported by physicians and patients prior to 1993, the authors of the review concluded that desmopressin produces few, mostly mild, adverse effects in children treated for nocturnal enuresis (Hjalmas 1993).

Water intoxication is potentially the most serious complication. It is associated with over-drinking at bedtime, and its symptoms include headache, nausea, hyponatraemia, cerebral oedema and convulsions. Current guidelines recommend that not more than 240 ml (8 ounces) of fluid should be consumed on any night when desmopressin is used (Bernstein 1997; Robson 1994; Robson 1996).

OBJECTIVES

To determine the effects of desmopressin for the treatment of children with nocturnal enuresis.

The following comparisons were made:
(1) desmopressin versus no active treatment / placebo;
(2) lower versus higher doses of desmopressin;
(3) oral versus nasal administration of desmopressin;
(4) desmopressin versus other drugs, alone or in combination;
(5) desmopressin alone versus alarm treatment alone;
(6) desmopressin alone versus desmopressin supplemented by alarm treatment;
(7) desmopressin supplemented by alarm treatment versus alarm treatment alone;
(8) desmopressin versus behavioural methods, alone or in combination;
(9) desmopressin versus complementary treatment .

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials of desmopressin with any comparable control groups for the treatment of nocturnal enuresis.

Types of participants

Children (as defined by trialists, usually as less than 16 years of age) suffering from nocturnal enuresis.

Types of interventions

Any trial that used desmopressin in at least one arm of the study.

Comparisons were made with no active treatment, other types of drugs, and alarm or behavioural interventions, either alone or in combination with desmopressin.

Types of outcome measures

The outcomes considered in this review were:

- mean number of wet nights per week during treatment;
- number of children failing to attain 14 consecutive dry nights during treatment;
- mean number of wet nights per week when children were followed up after treatment ends;
- number of children failing during treatment and/or relapsing after treatment ends;
- adverse effects.

Search methods for identification of studies

This review has drawn on the search strategy developed for the Incontinence Review Group. Relevant trials were identified from the Group's Specialised Register of controlled trials which is described, along with the group search strategy, under the Incontinence Group's details in *The Cochrane Library* (For more details please see the 'Specialized Register' section of the Group's module in The Cochrane Library). The register contains trials identified from MEDLINE, CINAHL, the Cochrane Central Register of Controlled Trials (CENTRAL) and hand searching of journals and conference proceedings. The Incontinence Group Specialised Trials Register was searched using the Group's own keyword system. The search terms used were:

({design.cct*} OR {design.rct*})
AND
{topic.enuresis*}
(All searches were of the keyword field of Reference Manager 9.5N, ISI ResearchSoft.)

Date of the most recent search of the register for this review: 10 May 2006.

The trials in the Incontinence Group's trials register are also contained in CENTRAL.

The reference list of a previous systematic review of enuresis treatments was also searched (Lister-Sharp 1997).

No language restriction or other limits were imposed on the searches.

Data collection and analysis

Identification of primary studies

The titles, and where possible, abstracts of all studies located by the searches were checked to identify any potentially relevant studies. Full papers were then obtained and assessed to identify those which met the inclusion criteria.

Quality assessment

A range of both general and more specific quality issues were noted, including:

- level of concealment of random allocation in the trials;
- whether data to assess the comparability of groups at baseline were given, including baseline levels of wetting;
- use of a 'washout' period if a crossover design was employed;
- intention-to-treat analysis;
- whether outcomes were clearly defined;
- blinding;
- a follow up of at least three months;
- the use of appropriate statistical techniques;
- whether useful data (e.g. means and standard deviations) were presented;
- whether children with daytime wetting were specifically excluded;
- whether children who had physical (organic) causes for their enuresis were specifically excluded.

Data extraction

The data were extracted using a standard form. Included data were processed as described in the Cochrane Reviewers' Handbook (Clarke 2003). Where appropriate, the results were converted to the mean and standard deviation of the number of wet nights per week; the number of children failing to achieve cure during treatment, defined as 14 consecutive dry nights; or the number of children who were not cured during treatment plus those who relapsed after stopping active treatment (to allow for possible differences in initial

'success' rates). When a mean value was reported with no standard deviation, we entered the data into 'Other Data Tables'.

Data analysis

We calculated, where possible, weighted mean differences (WMD) and relative risks (RR) plus 95% confidence intervals (CI). A fixed effect model was used to calculate the pooled estimates and the 95% CIs (Berlin 1989). The WMDs were weighted by the inverse of the variance and reported as differences in the number of wet nights per week. Negative values indicated fewer wet nights in the intervention group at the left-hand side of the tables. Differences between trials were further investigated when statistically significant heterogeneity was apparent either at the 10% probability level, using the chi squared test or assessment of the I-squared statistic (Higgins 2003), or from visual inspection of the results. If there was no obvious reason for the heterogeneity, or it persisted despite the removal of outlying trials, a random effects model could have been used.

Crossover trials were indicated by the symbol # after the trial ID. These were analysed as if they were parallel groups, but a sensitivity analysis was carried out by excluding these trials to determine if their inclusion biased the findings.

RESULTS

Description of studies

Of 75 studies identified as potentially relevant, 28 were excluded: 21 were not randomised controlled trials (RCTs); five included some adults with detrusor overactivity or daytime wetting, or both; one did not use desmopressin therapeutically (Bogaert 2005); and one switched children between treatment groups. In this minor update (Issue 3 2006), 2 of the 28 were new excluded studies (*see* Characteristics of Excluded Studies). Of the remaining included trials, 18 (Bradbury 1995; Faraj 1999; Folwell 1997#; Hamano 2000; Kahan 1998; Leebeek 2001; Longstaffe 2000; Muller 2001#; Natochin 2000; Neveus 1999#; Radmayr 2001; Rodriguez 2001; Schulman 2001a; Schulman 2001b; Sener 1998; Skoog 1997; Vertucci 1997; Yap 1998#) were RCTs added in the previous update (Glazener 2002). Two others (Dimson 1986#; Stenberg 1994#) had been excluded in the first published version of this review (Glazener 2000), and one more was added in the second update (Gibb 2004). In the third update (Issue 3 2006), a further five RCTs have been added (Fera 2004; Hoashi 1995; Lee 2005; Ng 2005; Uygur 1997#).

The 47 included trials were described in 44 reports (three reports described two separate trials each). Seventeen trials used a crossover design (indicated by symbol #). All the trials, bar two (Rodriguez 2001; Hoashi 1995), gave measures of baseline wetting, and all but three specifically excluded children with organic causes of enuresis (Fera 2004; Radmayr 2001; Yap 1998#). However, all three of these trials included only children with monosymptomatic nocturnal enuresis, and excluded children with daytime wetting (Fera 2004; Radmayr 2001; Yap 1998#). In general, sample sizes were small, ranging from 10 to 182 with an average of about 73 children. Out of a total of 3448 children, 2210 received treatment with desmopressin.

Participants

Two studies included some older children or adults (Janknegt 1997; Rittig 1988#), while another focused on adolescents who had failed previous treatment (Stenberg 1994#). Only seven of the trials excluded children who had previously received treatment for their enuresis (Faraj 1999; Fera 2004; Kahan 1998; Muller 2001#; Ng 2005; Radmayr 2001; Sener 1998). The remainder either failed to report this factor (9 trials) or included some children who had failed previous drug or behavioural treatments (31 trials). Of the latter, all the children in one trial had previously failed to improve with desmopressin (Gibb 2004). In another trial, a baseline trial of desmopressin was used to select out those children who failed to respond to desmopressin: only responders were enrolled in the crossover RCT (Uygur 1997#).

Dosage of desmopressin

Some trials used dose titration until dry nights were achieved (Birkasova 1978#; Faraj 1999; Fera 2004; Hamano 2000; Lee 2005; Radmayr 2001; Rittig 1988#; Rodriguez 2001; Rushton 1995; Schulman 2001b; Stenberg 1994#; Terho 1991#; Uygur 1997#), or compared a variety of doses of active drug (Kjoller 1984; Janknegt 1990#; Janknegt 1997; Miller 1990a; Miller 1990b; Neveus 1999#; Schulman 2001a; Skoog 1997). One reduced the dose from 40 µg to 20 µg for the second three weeks of the trial (Leebeek 2001).

Route of administration and comparators

Intranasal administration was used in all but ten of the trials: oral tablets were specified in ten (Fera 2004; Janknegt 1997; Lee 2005;Neveus 1999#; Ng 2005; Schulman 2001a; Schulman 2001b; Skoog 1997; Stenberg 1994#; Yap 1998#), and two different routes of administration were compared in one (Fjellestad 1987#). Twenty trials included other interventions:

- other drugs (Burke 1995; Hoashi 1995; Holt 1986; Lee 2005; Natochin 2000; Sener 1998; Vertucci 1997);
- alarms (Bradbury 1995; Faraj 1999; Gibb 2004; Leebeek 2001; Longstaffe 2000; Ng 2005; Rodriguez 2001; Sukhai 1989#; Wille 1986);
- other behavioural treatment (Fera 2004; Hamano 2000; Kahan 1998); and
- complementary treatment (laser acupuncture) (Radmayr 2001).

One ongoing trial has yet to be completed (Hjalmas 2001).

Risk of bias in included studies

Of the 47 identified RCTs which included desmopressin in at least one arm, only 15 described a secure randomised method of allocation (e.g. by computer allocation or use of sealed opaque envelopes) (Birkasova 1978#; Bradbury 1995; Burke 1995; Dimson 1986#; Folwell 1997#; Leebeek 2001; Longstaffe 2000; Neveus 1999#; Ng 2005; Schulman 2001a; Schulman 2001b; Stenberg 1994#; Sukhai 1989#; Uygur 1997#; Yap 1998#). A further 31 trials did not provide adequate details for this to be assessed (although some used double-blind placebo controls and others were crossover trials), and one trial used a quasi-randomised method (Natochin 2000).

There were 17 crossover trials, identified by the symbol # (Birkasova 1978#; Dimson 1986#; Fjellestad 1987#; Folwell 1997#; Janknegt 1990#; Muller 2001#; Neveus 1999#; Post 1983a#; Post 1983b#; Rittig 1988#; Stenberg 1994#; Sukhai 1989#; Terho 1984#; Terho 1991#; Tuvemo 1978#; Uygur 1997#; Yap 1998#). One other crossover trial compared desmopressin with imipramine, but only results from the first arm of the trial were used, which in effect formed parallel

groups (Vertucci 1997). Because of their crossover design, none of the crossover trials could address longer-term post-treatment effects. A further 21 trials used double-blind placebos to ensure blinding to treatment (Aladjem 1982; Burke 1995; Gibb 2004; Hoashi 1995; Holt 1986; Janknegt 1997; Kahan 1998; Kjoller 1984; Leebeek 2001; Longstaffe 2000; Martin 1993; Miller 1990a; Miller 1990b; Natochin 2000; Rushton 1995; Schulman 2001a; Schulman 2001b; Segni 1982; Sener 1998; Skoog 1997; Uygur 1997#). In the remainder of the studies, blinding to treatment allocation was not possible because the treatments were too dissimilar.

Two trials failed to report systematic baseline measures of wetting (Hoashi 1995; Rodriguez 2001), and three failed to exclude children with organic (physical) causes for their bed-wetting (Fera 2004; Radmayr 2001; Yap 1998#), but all these trials excluded children with daytime wetting. Three trials included some children with daytime wetting but excluded children with organic (physical) causes (Bradbury 1995; Gibb 2004; Martin 1993). Daytime wetting was specifically excluded or reported separately in 27 trials, and not mentioned in another 17.

Only three trials reported using a washout period between the two arms of a crossover trial (Fjellestad 1987#; Sukhai 1989#; Yap 1998#), while another interposed a 'placebo' arm between the first and second active arms (Janknegt 1990#). Children who did not respond in one trial (Schulman 2001a) received placebo treatment during a two-week washout phase before being randomly assigned again in a second trial (Schulman 2001b).

Ten trials reported continuous data without a measure of dispersion such as a standard deviation (Dimson 1986#; Fjellestad 1987#; Leebeek 2001; Miller 1990a; Miller 1990b; Muller 2001#; Rittig 1988#; Terho 1991#; Uygur 1997#; Vertucci 1997). Further data are being sought from the authors of some trials. Only two of the included trials provided a power calculation of the sample size, which helps to define the minimum sample size required to detect a true difference between the treatment groups (Janknegt 1990#; Leebeek 2001).

Effects of interventions

(1) Twenty nine trials compared desmopressin with placebo treatment (Aladjem 1982; Birkasova 1978#; Dimson 1986#; Fjellestad 1987#; Folwell 1997#; Janknegt 1990#; Kjoller 1984; Longstaffe 2000; Martin 1993; Miller 1990a; Miller 1990b; Muller 2001#; Natochin 2000; Neveus 1999#; Post 1983a#; Post 1983b#; Rittig 1988#; Rushton 1995; Schulman 2001a; Schulman 2001b; Segni 1982; Sener 1998; Skoog 1997; Stenberg 1994#; Terho 1984#; Terho 1991#; Tuvemo 1978#; Uygur 1997#; Yap 1998#);
(2) Two trials compared oral with nasal administration (Fjellestad 1987#; Faraj 1999);
(3) Seven trials compared desmopressin with tricyclic or other drugs (Burke 1995; Hoashi 1995; Holt 1986; Lee 2005; Natochin 2000; Sener 1998; Vertucci 1997);
(4) Nine trials compared desmopressin with alarms (Bradbury 1995; Faraj 1999; Gibb 2004; Leebeek 2001; Longstaffe 2000; Ng 2005; Rodriguez 2001; Sukhai 1989#; Wille 1986);
(5) Three trials compared desmopressin with behavioural interventions (Fera 2004; Hamano 2000; Kahan 1998);
(6) One trial compared desmopressin with laser acupuncture (Radmayr 2001).

1. Desmopressin versus no active treatment / placebo (see Comparisons 01 and 02, Other Data Tables 01)

Desmopressin was better than placebo treatment in achieving fewer wet nights per week during treatment and more children cured during treatment. Desmopressin was better (fewer wet nights per week) at doses of 10 µg in two trials (WMD -2.30; 95% CI -3.42 to -1.18); 20 µg in 12 trials (WMD -1.34; 95% CI -1.57 to -1.11); 40 µg in six trials (WMD -1.33; 95% CI -1.67 to -0.99); and 60 µg in two trials (WMD -1.50; 95% CI -1.92 to -1.08, Comparison 01.01). This held true in a sensitivity analysis when the crossover trials were excluded (e.g. WMD for 20 µg in seven trials -1.21; 95% CI -1.49 to -0.95, Comparison 08.01). Thus, desmopressin significantly reduced bed-wetting by about one to two nights a week, irrespective of whether the crossover studies were included. There were also fewer wet nights during desmopressin treatment in trials which used variable doses of the drug (Birkasova 1978#; Rushton 1995), or in trials which failed to provide standard deviations (Other Data Tables 01.02).

Ten trials reported the number of children cured (defined as achieving 14 consecutive dry nights) while taking either desmopressin or placebo. Despite differences in desmopressin dose, the trials were consistent, suggesting that desmopressin increased the chances of cure (RR for failure with 20 µg in five trials was 0.84; 95% CI 0.79 to 0.91: RR for 40 µg in six trials was 0.81; 95% CI 0.74 to 0.88: RR for 60 µg in two trials was 0.94; 95% CI 0.89 to 0.99, Comparison 01.03). A sensitivity analysis excluding the crossover trials supported these findings (Comparison 08.03).

However, the data suggest that this effect was not sustained after treatment had finished. In four trials (Aladjem 1982; Kjoller 1984; Miller 1990a; Miller 1990b), there was little difference between the groups in terms of wet nights per week, but the trials were small, the confidence intervals were wide, and two trials did not report standard deviations (Comparison 01.04, Other Data Tables 01.05). Only one small trial reported relapse rates: all the children either failed to respond to treatment or relapsed afterwards (Comparison 01.06) (Dimson 1986#).

2. Lower versus higher doses of desmopressin (see Comparison 03, Other Data Tables 03)

Eight small trials compared different doses of desmopressin with each other (Janknegt 1990#; Janknegt 1997; Kjoller 1984; Miller 1990a; Miller 1990b; Neveus 1999#; Schulman 2001a; Skoog 1997). Two of these trials were crossovers and two did not report standard deviations. There was some evidence that a higher dose was more likely to reduce the numbers of wet nights than a lower dose (e.g. for 20 µg versus 40 µg the WMD for wet nights during treatment was 0.42; 95% CI -0.01 to 0.84: for 20 µg versus 60 µg the WMD was 0.72; 95% CI 0.3 to 0.14, Comparison 02.01, Other Data Tables 02). However, there was no difference in cure rates (Comparison 02.03). One trial reported no difference between two oral doses, but it did not provide any useable data (Janknegt 1997).

3. Oral versus nasal administration of desmopressin (see Comparison 04, Other Data Tables 04)

Only one study compared oral (200 µg) and nasal (20 µg) administration of desmopressin (Fjellestad 1987#). This was a crossover trial which did not provide standard deviations and involved only 20 children. There were insufficient data to judge whether the two routes were equally effective. Nasal discomfort (two children) and epistaxis (three children) were reported with

nasal administration. This did not appear to be specifically linked to desmopressin because it was reported equally by patients from both the other groups who received placebo nose drops (Fjellestad 1987#).

4. Desmopressin versus other drugs (see Comparison 05, Other Data Tables 05)

Seven trials compared desmopressin with other drugs: amitriptyline (Burke 1995); imipramine (Hoashi 1995; Holt 1986; Lee 2005; Vertucci 1997); indomethacin (Natochin 2000); and diclofenac (Sener 1998). One trial included an arm which combined amitriptyline with desmopressin (Burke 1995) and another combined desmopressin with oxybutynin (Lee 2005). In two small separate studies, desmopressin performed better than indomethacin (WMD for wet nights per week -1.45; 95% CI -2.37 to -0.53, Comparison 04.01.05) (Sener 1998) and diclofenac (RR for failure to achieve 14 dry nights was 0.52; 95% CI 0.30 to 0.89, Comparison 04.02.03) (Natochin 2000) during treatment, but there was no information about relapse rates after treatment ended. There was not enough evidence to clarify whether desmopressin was better than amitriptyline or oxybutynin added to desmopressin: the sample sizes were too small to address the issue reliably, the follow-up information was scant, and the confidence intervals were wide. However, more children achieved dry nights with desmopressin than imipramine during treatment (RR for failure to achieve 14 dry nights 0.44, 95%CI 0.27 to 0.73, Comparison 05.02.04) (Lee 2005) but there was no information about subsequent relapse.

5, 6, 7. Desmopressin and alarms

Nine trials compared desmopressin with alarm interventions (Bradbury 1995; Faraj 1999; Gibb 2004; Leebeek 2001; Longstaffe 2000; Ng 2005; Rodriguez 2001; Sukhai 1989#; Wille 1986). In four trials, desmopressin was compared with an alarm alone (Faraj 1999; Longstaffe 2000; Ng 2005; Wille 1986). In three other studies, the children used alarms in both arms of the trials supplemented with either desmopressin or placebo (Gibb 2004; Leebeek 2001; Sukhai 1989#), the latter in a double-blind crossover design with a two-week washout period. In a further three trials, children used alarms in both arms of the trial, supplemented by desmopressin in one arm (Bradbury 1995; Ng 2005; Rodriguez 2001).

5. Desmopressin alone versus alarm treatment alone (see Comparison 06)

In four trials, desmopressin was compared with an alarm alone (Faraj 1999; Longstaffe 2000; Ng 2005; Wille 1986). One small trial reported that at the end of the first week of treatment, there were 1.7 fewer wet nights per week with desmopressin treatment than with alarm treatment (WMD -1.7; 95% CI -2.95 to -0.45, Comparison 06.01.01) (Wille 1986). In the final week (after three months) there was no significant difference between desmopressin and alarm groups in terms of wet nights per week (WMD 0.52, 95% CI -0.32 to 1.36, Comparison 06.01.02) (Ng 2005; Wille 1986) or in numbers remaining wet (RR 1.07, 95%CI 0.83 to 1.36, Comparison 06.02.01) (Faraj 1999; Longstaffe 2000; Ng 2005). However, the relapse rate was significantly less after the end of alarm treatment (40/62, 65% after desmopressin versus 26/57, 46% after alarm, RR 1.42, 95% CI 1.05 to 1.91, Comparison 06.03.01) (Wille 1986; Ng 2005). Where combination of data was possible, the heterogeneity was high.

6. Desmopressin alone versus desmopressin supplemented by alarm treatment (see Comparison 07)

One small trial tested the effect of adding alarm treatment to desmopressin (Ng 2005). The data were too few to draw reliable conclusions.

7. Desmopressin supplemented by alarm treatment versus alarm treatment alone (see Comparison 08)

Six trials addressed this comparison (Bradbury 1995; Gibb 2004; Leebeek 2001; Ng 2005; Rodriguez 2001; Sukhai 1989#). Desmopressin combined with alarm treatment was associated with fewer wet nights than alarms alone in four trials (WMD -0.83, 95% CI -1.11 to -0.55, Comparison 08.01.01), whether a placebo was used (Gibb 2004; Sukhai 1989#) or not (Bradbury 1995; Ng 2005). However, this was not reflected in failure rates during treatment: RR for the number of children failing to achieve 14 dry nights was 0.88; 95% CI 0.73 to 1.05, Comparison 08.02.01) with placebo (Gibb 2004; Leebeek 2001) or without placebo (Bradbury 1995; Ng 2005; Rodriguez 2001): the heterogeneity was high.

After treatment stopped, there were no statistically significant differences in the combined failure and relapse rate: RR 0.91, 95% CI 0.76 to 1.08, Comparison 08.03.01) with placebo (Gibb 2004; Leebeek 2001) or without (Bradbury 1995; Ng 2005). However, the trials were small; one was a crossover with a short duration of treatment (Sukhai 1989#); the confidence intervals were wide; and follow-up results were not available for two trials (Rodriguez 2001; Sukhai 1989#).

8. Desmopressin versus behavioural methods, alone or in combination (see Comparison 09)

Three small trials compared desmopressin alone or in combination with other behavioural methods of managing enuresis (Fera 2004; Hamano 2000; Kahan 1998). The interventions were so dissimilar (retention control training alone in one (Hamano 2000), a complex package of psychological therapy with retention control training in another (Kahan 1998) and a mix of toileting, waking with alarm clock, pelvic floor training and diet and fluid changes in the third (Fera 2004) that data could not be combined. Thus each comparison was addressed by single arms of the trials only.

There was insufficient evidence to compare desmopressin with retention control training alone (Comparisons 09.01.01, 09.02.01, 09.04.01) (Hamano 2000) or with a complex intervention (Comparisons 09.01.04, 09.02.04) (Fera 2004). There was conflicting evidence about the effects of the complex package during treatment (Comparisons 09.01.02 and 03, and 09.02.02 and 03) and afterwards: children recorded fewer wet nights after desmopressin supplemented by the complex package of psychological and behavioural methods, compared to desmopressin alone (WMD -2.10; 95% CI -2.67 to -1.53, Comparison 09.03.02) but this did not reflect in lower failure/relapse rates (RR 0.98; 95% CI 0.91 to 1.06, Comparison 09.04.02) (Kahan 1998).

9. Desmopressin versus complementary treatment (see Comparison 10)

One small trial compared desmopressin with laser acupuncture (Radmayr 2001). However, results were only reported at six months after completing the trial. There was no difference between the groups at follow up, but the numbers were too small to draw reliable conclusions.

Adverse effects

Adverse effects of desmopressin reported amongst 1057 children in 14 trials included (number of events in brackets): anorexia (5), bad taste (2), headache (12), nasal discomfort (20), nosebleeds (6), rash/dermatitis/oedema (6), sight disturbance (1), vomiting (3) and other minor problems (44). Some trials reported that side effects (headaches, stomach ache and nasal symptoms) were equally common with active and placebo treatment (Fjellestad 1987#; Folwell 1997#; Janknegt 1990#), or with desmopressin and tricyclics (Hoashi 1995) or were not due to treatment (Schulman 2001a; Schulman 2001b). Four trials reported that most minor side effects resolved as the trials continued (Schulman 2001a; Schulman 2001b; Skoog 1997; Stenberg 1994#). Side effects were not mentioned in nine trials (Faraj 1999; Fera 2004; Janknegt 1997; Longstaffe 2000; Muller 2001#; Neveus 1999#; Post 1983a#; Post 1983b#; Rodriguez 2001). The remaining 17 trials reported that there were no adverse effects in a further 865 children (Aladjem 1982; Birkasova 1978#; Burke 1995; Kjoller 1984; Leebeek 2001; Natochin 2000; Ng 2005; Radmayr 2001; Rushton 1995; Segni 1982; Sener 1998; Sukhai 1989#; Terho 1984#; Terho 1991#; Tuvemo 1978#; Uygur 1997#; Yap 1998#). One of these trials involved another drug, amitriptyline, with and without desmopressin (Burke 1995). When reported, more adverse effects were associated with tricyclics (83/480, 17.3 per 100 patients (Glazener 2004e)) than with desmopressin (70/1319, 5.3 per 100 patients).

DISCUSSION

This is the third update of the desmopressin review, including 25 new trials identified since the original review was published in 1997 (Lister-Sharp 1997). The quality of the trials was often poor: small numbers of children were assessed; reporting of data and the method of randomisation were inadequate; and follow up was short or non-existent. In the crossover trials there was a lack of washout phases and, by their design, no follow up was possible. In particular, little information was available about comparisons with non-drug interventions. However, all trials focused on children who did not have an organic cause for their enuresis: in the trials which did not specifically exclude organic causes, any children who had daytime wetting were excluded. Only two trials failed to objectively assess baseline wetting. Seven trials selected children who had not had previous enuresis treatment. The majority of the trials (30/46) included at least some children who had failed with previous treatment, and therefore had been referred to specialist clinics; the remainder did not specify past treatment.

Desmopressin compared with placebo

There was clear evidence that desmopressin reduced bed-wetting by approximately one to two wet nights per week, compared to placebo. In addition, people receiving desmopressin were almost twice as likely as those receiving placebo to achieve at least 14 consecutive dry nights. However, after treatment stopped, the limited evidence available suggested that this improvement was not sustained. Ten crossover trials were analysed as if they were parallel groups. However, a sensitivity analysis showed that their exclusion did not affect the conclusion that desmopressin significantly reduced bed-wetting by one to two nights a week while on treatment. Crossover trials were unable to contribute follow-up data after the end of the treatments because the children had received both trial treatments by then.

Dose of desmopressin and route of administration

There were insufficient data to reliably assess whether a higher dose of desmopressin was more effective than a lower dose. To minimise side effects and costs, the lowest dose should be used. In practice, clinicians would increase the dose until the lowest effective dose is achieved. If a higher dose is used with no incremental improvement, the dose should be returned to the lowest effective level. There was not enough evidence to judge whether oral and nasal administration were equally effective, but eight trials used the oral route with no apparent difference in effectiveness. This suggests that equivalent doses may be comparable, irrespective of the route of administration.

Desmopressin compared with other drugs (see also review of tricyclics for enuresis, Glazener 2004e)

The four trials comparing desmopressin with amitriptyline or imipramine were too small to provide definitive results. Desmopressin is more expensive than imipramine, but imipramine has more side-effects, some of them potentially serious. In two other small trials, desmopressin was better than either indomethacin or diclofenac during treatment, but there was no follow-up information (Natochin 2000; Sener 1998).

Desmopressin compared with alarms (see also review of alarms for enuresis Glazener 2004a)

Although nine trials including desmopressin and alarm treatments were identified, the findings were difficult to interpret because of the poor quality (small size and dissimilar outcome measures) and variation in interventions (with or without desmopressin or placebo supplementation) of the trials.

In direct comparisons of desmopressin with alarm treatment, the initial advantage of desmopressin (fewer wet nights) was not sustained: children using alarms had fewer wet nights by the end of the trial, and the subsequent relapse rate was lower after alarm treatment (Wille 1986, Ng 2005). While another two small trials demonstrated no significant difference in the failure rate during treatment, follow-up information was not available (Bradbury 1995; Rodriguez 2001).

There is a move towards combining behavioural and drug interventions (Howe 1992). The rationale is that the rapid onset of action of drugs will augment the more gradual treatment effect of alarms (Sukhai 1989#). Using low doses of desmopressin as an adjunct to alarm treatment might also be used to ensure that the child only wets the bed once each night, which minimises changes of bedding (Djurhuus 1992). The alternative argument, however, is that by using a drug to reduce the wetting, the child has fewer chances to learn behavioural control with the alarm (Gibb 2004). Although there were indeed fewer wet nights during combination treatment compared with desmopressin alone (Comparison 07.01.01, Ng 2005) and alarm alone (Comparison 08.01.01, Bradbury 1995; Gibb 2004; Ng 2005; Sukhai 1989#), it was not possible to judge whether this was reflected in lower failure or relapse rates (Comparison 07.03.01, Ng 2005; and Comparison 08.03.01, Bradbury 1995; Gibb 2004; Leebeek 2001; Ng 2005). This evidence was limited by small numbers and disparate interventions. The use of desmopressin as an adjunct to alarm treatment may be a good way of easing the initial weeks of alarm treatment or for giving families a break, but it is uncertain whether

this helps in the long term. This needs to be evaluated by further research.

Desmopressin compared with other behavioural methods

There was no clear evidence to support the use of a complex package of behavioural methods, delivered either with or without desmopressin, in terms of numbers of children cured. Although desmopressin may have contributed to a reduction in the number of wet nights per week during treatment and afterwards, there was no difference in cure rates. This finding needs to be verified with further research. There was not enough evidence to compare desmopressin with retention control training alone.

Desmopressin compared with complementary treatments

In one small trial (comparing desmopressin with laser acupuncture), there was no difference in the failure rate six months after the end of the trial, but the numbers were too small to reliably compare the groups (Radmayr 2001). However, in view of the lack of effect of desmopressin after treatment stops (see comparison of desmopressin with placebo above, Comparisons 01.04 and 01.06, Other Data Tables 01.05), it was not possible to determine if the apparent cure of three quarters of the children in both groups was an effect of both treatments or due to spontaneous cure with time.

Other considerations

Relevant outcome measures

Most trials reported outcome criteria in terms of number of wet nights per week. The number achieving 14 dry nights was reported less often, and few trials provided follow-up data or relapse rates. It is likely that parents would prefer a treatment that cured the problem in the long term, rather than simply decreasing the frequency of wet nights during treatment. However, reported outcome measures may reflect different aims of treatment: drugs could be used as a way to reduce the frequency of wetting for a specific purpose such as nights away from home (e.g. on a 'dry for camp' basis, for holidays or staying with friends (Meadow 1989)). Some families may find desmopressin useful over winter to overcome laundry problems.

Daytime wetting / organic causes

Only including trials that definitely excluded all children with daytime wetting would have severely limited the review. Only 26 of the 46 trials specifically excluded children with diurnal wetting; the remainder either failed to mention it (17 trials) or failed to exclude it (3 trials). All but one of the trials specifically excluded children with known organic causes for their enuresis. It is likely that the underlying pathologies of monosymptomatic bed-wetting and mixed night and day wetting differ. The former group might be expected to respond better to treatment aimed at the symptom of bed-wetting, whereas the latter might respond better to treatment aimed at the underlying pathology (e.g. urinary tract infection, unstable bladder). Alternative managements for these conditions need to be reviewed.

Settings and previous treatment

It should not be assumed that the interventions that are most effective in the trial situation are always the treatments of choice in the clinical situation. Most of the included trials have recruited children from enuresis clinics or are hospital based. Twenty of the trials included at least some children who had already failed previous treatments and were being referred for further advice. These participating families may be especially motivated to tackle bed-wetting. In addition, strict inclusion or exclusion criteria were imposed in many of the trials. Consequently, the children involved were not necessarily representative of the wider population of bed-wetters. Factors that made treatment more likely to be successful included: older age, fewer initial wet nights and larger functional bladder capacity (Rushton 1996).

Adverse effects

The reporting of adverse effects varied. In some trials they were not mentioned, while in others they were reported just as often in placebo groups. Some trials reported no adverse effects in any treatment group. All trials reported that the adverse effects of desmopressin were minor and did not require the treatment to cease. Although there appear to be fewer adverse reactions associated with desmopressin than tricyclic drugs, these are rare but can be serious. The risk of water intoxication should be minimised by restricting evening fluid intake on the nights that desmopressin is used (Bernstein 1997; Robson 1994; Robson 1996). Tricyclics are the most common cause of fatal poisoning in children (Parkin 1972). Overdose with tricyclics may occur accidentally or when children believe that a greater dosage gives a better effect (Wille 1986).

Costs

In the United Kingdom, 16 weeks of drug treatment (the usual time allowed for fourteen consecutive dry nights to be attained using an alarm (Butler 1991)) costs (BNF 2002):

- UK£78 for desmopressin nasal spray (20 µg per night) or UK£116 for desmopressin tablets (200 µg);
- UK£4 for imipramine hydrochloride (25 mg tablet per night) or UK£14 for imipramine syrup (25 mg);
- enuresis alarms (including batteries and sensor) typically cost UK£33.60, although alarms but not sensors (UK£12) may be reused several times.

Although treatment with tricyclic or related drugs is considerably less expensive than alarms or desmopressin, this does not take into account the administrative or human costs involved in using alarms. Alarm systems may not be returned to clinics and have to be followed up. Alarm treatment is accompanied by broken nights for various family members until success is attained. The Guidelines on Minimum Standards of Practice (Morgan 1993) suggest that follow-up supervisory contacts should occur at least every three weeks, with medication reviewed at least monthly. However, this must be considered in light of the lower likelihood of relapse after completing alarm treatment, compared with after desmopressin, tricyclics or related drugs, and the potential for adverse effects with tricyclics.

AUTHORS' CONCLUSIONS

Implications for practice

Desmopressin rapidly reduced the number of wet nights per week, compared with placebo in children with monosymptomatic nocturnal enuresis, but this effect was not sustained after treatment

stopped. Only two small RCTs followed up children treated with desmopressin or an enuresis alarm; those treated with the alarm were more likely to achieve long-term success, but this needs to be confirmed in further research. Children who used alarms supplemented with desmopressin initially had fewer wet nights compared to after alarms alone, but this was not reflected in better cure rates or reduced relapse rates after stopping treatment. Potential difficulties, such as the commitment and time needed to attain success, need to be discussed with families before embarking on alarm treatment.

Treatment with desmopressin is considerably more expensive than with tricyclic drugs, but is associated with fewer adverse effects and less risk of fatal overdose. Although alarm interventions are intermediate in cost and are more disruptive in the short term, they do not have the same risk of side effects.

Patients and their families need to be warned about potential adverse effects associated with desmopressin. In particular, children should be advised not to drink more than 240 ml (8 ounces) of fluid on any night that desmopressin is given in order to avoid the possible risk of water intoxication.

Implications for research

More trials comparing desmopressin with other methods of management are required, especially with alarms, tricyclic drugs, and other behavioural interventions such as lifting, star charts, reward systems and fluid deprivation. Further trials of desmopressin versus placebo should address the issue of whether the benefits are sustained after stopping treatment. Such trials should focus on children who do not have organic causes of bed-wetting, and should include adequate assessment of baseline levels of wetting.

The trials should use uniform outcome measures such as: the number of wet nights during treatment and after the end of treatment; the number of children achieving 14 consecutive dry nights (cure rate); adverse effects; acceptability of treatment; compliance; and especially relapse rates.

The trials should include children from a variety of backgrounds and populations, particularly those children who have not already failed previous treatment, in order to increase the generalisability of the results. Important demographic factors that should be considered include previous treatment, age, presence of other organic pathology or daytime wetting and family circumstances, as well as co-existing psychological, emotional or behavioural problems. It has been suggested that not all interventions are suitable for all children. Therefore, further research is needed to determine which interventions are appropriate for which patient groups and under what circumstances (for example, as a short-term measure to cover nights away from home), in order to guide choice of treatment.

Children with daytime enuresis are more likely to have specific pathology, such as bladder dysfunction or urinary tract infections. Alternative managements for this condition need to be reviewed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aladjem 1982

Methods	RCT (double blind, method not specified) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned Follow up after 30 days
Participants	Number of children: 32 (boys: A:7, B:8) Previous treatment: 5/23 responded to chlorimipramine hydrochloride Mean age (years): A:10.5, B:10.0 (range 7-15) Baseline wetting: mean (SD) number of wet nights in 30: A:18.7 (6.5), B:21.3 (8.5) No significant difference between groups in urine osmolalities
Interventions	A (15): 10 µg DDAVP intranasally B (17): placebo as above
Outcomes	Mean (SD) number of wet nights out of 30: A:6.5 (9.2), B:18.8 (8.3) Number totally dry: A:6, B:1 Number of wet nights at follow up: A:15.7 (8.9), B:16.9 (9.4) Significant difference in response of children according to age Only those over 10 years became completely dry The only failures (n=3) were less than 10 years old Side effects: none reported Prompt response to DDAVP - as early as 1-3 days
Notes	Unclear about dropouts Short follow up Age effect suggested Inclusion criteria: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement

Aladjem 1982 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

Birkasova 1978#

Methods	RCT (double blind crossover) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned Follow up after 4-6 weeks
Participants	Number of children: 22 (14 boys) Previous treatment: all had failed to respond to psychotherapy and a regimen that included fluid deprivation after 5 pm Some had previously been unsuccessfully treated with imipramine Exclusion criteria: organic causes of enuresis Mean age (years): 6.6 (range 4-12) Baseline wetting: mean (SD) wet beds per fortnight: 10.6 (4.9)
Interventions	A: 10 µg DDAVP drops intranasally at bedtime B: 40 µg DDAVP drops intranasally at bedtime C: placebo Duration of treatment: 2 weeks in each arm
Outcomes	Mean (SD) number of wet nights per fortnight A+B:4.2 (4.5) C:11 (4.4) Side effects: none reported 5 patients receiving a higher dosage were totally dry 9 continued DDAVP single blind for 4 to 6 weeks then given placebo 7 remained dry without drug 1 wet once monthly and 1 returned to daily wetting 4 who had wet nightly continued on DDAVP for 3 more months by which time they were dry 1 had 1 wet night per fortnight and 1 had 1 wet night in 3 2 patients who were indifferent to wetting showed no response to DDAVP or placebo
Notes	No measure of comparability at baseline No washout period Not clear if intention to treat because no details of dropouts Subjects were very young High and low doses combined in analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

Bradbury 1995

Methods	RCT (quota allocation system based on age, baseline wetting, family or housing problems, gender, previous alarm use, daytime wetting and previous dry periods) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: No 6 month follow up

Bradbury 1995 *(Continued)*

Participants	Number of children: 71 (boys 48) Dropouts A: 3, B: 8 Inclusion criteria: nocturnal enuresis at least 1 night per week (40/71 = severe, >4 times per week) Exclusion criteria: neuropathic bladder, urinary tract abnormalities, cystic fibrosis, allergic rhinitis, deafness/ learning difficulties, UTI Previous treatment: 29 had used alarms
Interventions	A (36): desmopressin 40 µg intranasally and alarm (bell-and-pad or Mini Drinite) B (35): alarm alone Duration 6 weeks or until dry
Outcomes	Mean DRY nights per week: A: n=33, mean = 6.1, 95% CI 5.6-6.7; B: 27, 4.8, 4.0-5.6 Number not achieving 4 dry nights: A: 6/33; B: 11/27 Number failing or relapsing: A: 10/33; B: 14/27 Side effects: none reported Subgroup analysis in more severe group: A still better than B
Notes	Mini Drinite = body-worn alarm Relapsing = 2 wet nights in 2 weeks after 4 weeks dry Authors recommended using combined desmopressin and alarm only for children with severe wetting problems

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Burke 1995

Methods	RCT (multi-centre, double blind) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned
Participants	Number of children: 45 (boys: A:11, B:10, C:9) Dropouts: A:0, B:3, C:3 Inclusion criteria: age 6-17 years; at least 3 wet nights per week for preceding 3 month period and not dry for more than 6 months Exclusion criteria: enuresis treatment in preceding 6 months; nocturnal enuresis of neurogenic origin; urinary tract infection; abnormal urinalysis haematology or blood biochemistry; concomitant medication known to interfere with study medication Age, mean years (SD): A:8.6 (2.4), B:8.9 (2.5), C:8.9 (2.4) (range 6-14) Baseline wetting: mean (SD) number of wet nights per week: A:5.8 (0.9), B:6.0 (0.9), C:6.3 (0.9)
Interventions	A (14): amitriptyline hydrochloride (25 mg or 50 mg) B (17): desmopressin (20 µg) intranasally C (14): DDAVP and amitriptyline Duration of treatment: 16 weeks Follow up 12 weeks
Outcomes	Mean (SD) number of wet nights per week: A:3.3 (1.9), B:4.7 (1.7), C:3.3 (2.5) Number attaining cure: A:3, B:1, C:5 7 out of 8 children who were cured relapsed. The exception was treated with amitriptyline and DDAVP Follow up: mean (SD) number of wet nights per week: A:(n=10) 3.9 (2.9), B:(n=5) 3.8 (1.9), C:(n=8) 5.1 (3.2) Side effects: none reported

Burke 1995 *(Continued)*

	Most parents said all the drugs were easy to use
Notes	No significant difference between groups in terms of number, age, height and weight Trial prematurely halted due to one drug ceasing to be available Not stated if intention to treat Not full quota of subjects

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Dimson 1986#

Methods	RCT (double blind crossover) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned
Participants	Number of children: 17 (14 boys) Inclusion criteria: 3 with encopresis Exclusion criteria: UTI, organic disease (clinical or radiological) Previous treatment: failure to respond to tricyclics and alarms Age range 6-13 years Baseline wetting >50% wet nights in 2-week observation period
Interventions	A (17): 20 µg desmopressin intranasally B (17): matching placebo Duration of treatment 2 weeks
Outcomes	Mean wet nights per week: A: 117 in 2 weeks in 17 children (= mean 3.4/week); B: 169 in 2 weeks in 17 children (= mean 5.0/ week) Number not achieving 14 dry nights: A: 2 cured, 10 improved, 5 failed; B: 5 improved slightly, 12 failed Number failed or relapsed: A: 17/17; B: 17/17 Side effects: none reported (no overhydration, weight or BP change)
Notes	No washout period All children relapsed after end of trial No SDs

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Faraj 1999

Methods	RCT (random number tables, details not given) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes

Faraj 1999 *(Continued)*

Participants	Number of children: 135 Dropouts: 23 excluded for non-compliance, and 39 lost to follow up including 12 failed with alarms Inclusion criteria: monosymptomatic nocturnal enuresis, age >5 years Exclusion criteria: previous treatment with DDAVP or alarm, urological pathology, diurnal enuresis, UTI Age, mean years: 11.2 Baseline wetting: A 21% dry nights, B 14% dry nights
Interventions	A (62): desmopressin 20 µg intranasally increasing to 40 µg if response partial B (73): alarm (pad-and-bell) Duration of treatment 3 months. If failed at that time, changed to alternative arm
Outcomes	DRY nights at 3 months: A 85%; B: 90% Number not achieving 14 dry nights: A 12/39; B: 6/37 Side effects: not mentioned
Notes	No follow up No mention of adverse events

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Fera 2004

Methods	RCT (randomized in 2 groups) Systematic baseline measure of wetting: Yes Organic causes excluded: No Daytime wetting excluded: Yes Setting: Federal University of Sao Paulo
Participants	No. of children (boys): 30 (21) Dropouts: None Inclusion: monosymptomatic nocturnal enuresis, age over 5 years, no daytime wetting Exclusion: none mentioned Previous treatment: none Age, mean years (SD): 9.23 (1.85) Baseline wetting, mean (SD) wet nights in 2 weeks: 9.40 (3.40)
Interventions	A (15): DDAVP (desmopressin), titrated to maximum 0.4 mg at bedtime B (15): behavioural modification (dietary and fluid adjustment, voiding schedules, double voiding, bed-time toileting, alarm clock once at night, pelvic floor training, environmental modifications, changes in parents' attitudes, improvement of self-esteem, self care) Duration of treatment: 30 days Follow up: none
Outcomes	Wet nights during last 2 weeks of treatment N, mean (SD): A: 15, 7.27 (4), B: 15, 3.93 (3.32) 50% improvement: A: 7/15, B: 8/15 Complete failure: A: 5/15, B: 1/15 Adverse effects: not mentioned
Notes	Groups comparable at baseline on age, gender and baseline wetting No data for children 'cured' (14 consecutive dry nights)

Fera 2004 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Fjellestad 1987#

Methods	RCT (double blind, double dummy, cross over) Periods of treatment preceded and followed by one week of observation Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes Follow up after 1 week
Participants	Number of children: 30 (20 boys), 1 dropout Exclusion criteria: urinary tract infections; diurnal wetting; faecal soiling; neurological or urological abnormalities; 3+ wet nights a week during baseline Previous treatment: 69% tried one or more other treatment Age, mean (SD): 9.8 (2.5) (range 6-15) Baseline wetting: mean number of dry nights in week: 2.2 (SD 0.2)
Interventions	A: 200 µg oral desmopressin B: 20 µg intranasal desmopressin C: placebo tablets D: placebo nasal pipette Duration of treatment: 2 weeks placebo then 2 weeks each condition
Outcomes	During treatments mean number of dry nights: A:4, B:4.1, C:2.5 2 patients totally dry while taking tablets; 1 patient totally dry while using intranasal 9 children (31%) remained totally dry Side effects: no significant adverse effects but 2 patients complained of occasional nasal discomfort and 3 of epistaxis but no difference between placebo and active arms
Notes	Not reported if comparable groups Washout one week between each arm Not intention to treat Many results only given graphically Short follow up No SDs

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Folwell 1997#

Methods	RCT (double-blind crossover) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes

Folwell 1997# *(Continued)*

Participants	Number of children: 31 (22 boys), small number of adults Dropouts/not included: 6 Inclusion criteria: primary monosymptomatic enuresis, age over 6 years Exclusion criteria: diabetes, neurological or renal disease, steroids, diuretics, daytime wetting Previous treatment: failed on alarms, anticholinergics Age, mean years: 11.2 (SD 5.4)
Interventions	A: desmopressin 20 µg intranasal B: placebo 21 days each, then crossed over
Outcomes	Mean wet nights/week during trial: A: 3.24 (SE 0.45); B: 4.86 (0.35) Side effects: A: 1 nausea; B: 1 drowsy and vomiting
Notes	No washout period No follow up Groups reported to be comparable but data not given

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Gibb 2004

Methods	RCT (drug dispensed randomly by pharmacist) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: No Setting: Paediatric outpatients, Children's Hospital, Melbourne, Australia
Participants	Number of children (boys): 207/210 (A:64, B:78) Dropouts: 10 eligible children declined, incomplete data on A:9/101, B:17/106 but dropouts counted as failures for analysis Inclusion criteria: Non-responders to desmopressin treatment (<50% reduction in wet nights), age 6-16 years, wetting at least twice per week, some daytime wetting (A:11, B:8) Exclusion criteria: Neuropathic bladder, urinary tract abnormality, cystic fibrosis, allergic rhinitis, UTI in previous 2 weeks, imipramine or diuretics Previous treatment: some had alarm (A:37, B:32) or desmopressin (A:31, B:28) Age: mean 9.4 years (SD 2.08) Baseline wet nights in 28 days: A: 23.9 (SD 5.05), B: 23.7 (5.83)
Interventions	A (84/101): desmopressin (40 µg nasal spray) + alarm (pad and bell) B (85/106): placebo (nasal spray) + alarm (pad and bell) Duration of treatment: 8 weeks Follow up: 2 months
Outcomes	Cure = 28 dry nights, relapse = 2 wet nights in 2 weeks Wet nights during treatment (number, mean (SD)): A: 101, 1.8 (1.13), B: 106, 2.4 (1.53) Cure during treatment: A: 52/101, B: 51/106 P=0.63 (failed: A: 49/101, B: 55/106) Relapse after treatment stopped: A: 7, B: 3 Failed or relapsed: A: 56/101, B: 58/106

Gibb 2004 *(Continued)*

	Adverse effects: A: 1 (headache), B: 1 (nose bleed) Other: compliance same in both groups Cure in daytime wetting: A: 6/11, B: 3/8
Notes	Intention to treat analysis Groups comparable at baseline on age, wetting, gender, family history, secondary enuresis, daytime wetting and previous treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hamano 2000

Methods	RCT (method not given) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes Follow up 2 weeks
Participants	Number of children: 114 (88 boys) Dropouts: 18 (not wet or poor compliance) Inclusion criteria: primary monosymptomatic nocturnal enuresis, at least 4 times per week Exclusion criteria: neurological or physical abnormalities, UTI Age: 5-15 years, A: 9.2; B: 9.4 Baseline wetting (SD): A: 6.8 (0.7); B: 6.7 (0.9)
Interventions	A (54): DDAVP intranasally, 5 µg increasing to 20 if no response, decreasing when strongly responding B (60): retention control training; holding voiding once a day to increase bladder capacity Duration of treatment: 12 weeks
Outcomes	Wet nights per week (N, mean, SD): A: 54, 6.8 (SD 0.76); B: 60, 6.7 (0.87) Number not achieving 14 dry nights A: 33/54; B: 46/60 Relapsing after cure: A 17; B: 5 Failed or relapsing after trial: A: 50/54; B: 51/60 Side effects: adverse events infrequent: A: 2/54 (nasal discomfort); B: 0/60
Notes	Results presented according to functional bladder capacity but merged here Short follow up Groups comparable at baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hoashi 1995

Methods	RCT (randomly allocated in blocks of 4) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes

Hoashi 1995 *(Continued)*

	Setting: Day clinics at drug company
Participants	No. of children (boys): 231 (167) Dropouts: 7 not wet at baseline, 1 moved, 2 daytime wetting, 4 delayed treatment, 2 non-compliance Inclusion: wet 10/14 nights Exclusion: daytime wetting, organic causes, family disruption Previous treatment: no information Age: at least 6 years Baseline wetting: mean 12.8 wet nights in 2 weeks
Interventions	A (112): desmopressin 10 µg nasal drops + placebo tablet B (112): imipramine tablet (25 mg) + placebo nasal drops Duration of treatment: 4 weeks Follow up: none
Outcomes	Wet nights during treatment (N, mean, SE) At 2 weeks: A: 111, 9.5 (SE 0.5), B: 111, 9 (0.5) At 4 weeks: A: 109, 8.7 (SE 0.5), B: 109, 8 (0.5) Adverse effects causing stopping: A: 0, B: 1 Other adverse effects: Oedema, headache, sleepyness, insomnia, sleep disorder, dizziness, appetite loss, nausea, vomiting, diarrhoea, abdominal pain, eyelid swelling, rash, red eyelid, nose symptoms (itchy nose, bleeding nose, blocked nose, runny nose), fever, tiredness, shaking head, thirsty, dry lips Total number of side effects: A: 29/120, B: 29/118 Total number of children with side effects: A: 16/120, B: 16/118 Other outcomes: wetting score, side effect score, satisfaction score, overall score
Notes	Japanese language Data measured from graphs No follow up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Holt 1986

Methods	RCT (method not given, double-blind) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes
Participants	Number of children: 36 Inclusion criteria: 2 or more wet nights per week; age 8-12; Exclusion criteria: day time wetting; diabetes, insipidus or other chronic illness where need daily medication; other treatment for bed wetting Mean age (years): A:9.8, B:9.5 (range 8-12) Baseline wetting: wet bed 2 or more times per week
Interventions	A (19): imipramine 50 mg and placebo nasal spray B (17): intranasal desmopressin 20 µg and placebo tablets Duration of treatment: 4 weeks Follow up: 6 weeks
Outcomes	Results first 2 weeks of treatment: % reduction in wet nights: A:48%, B:45%

Holt 1986 *(Continued)*

	Results final 2 weeks of treatment: A:54%, B:32% Mean (SD) number of wet nights per first 14 days: A:4.9 (4.3), B:4.8 (4.0) Mean (SD) number of wet nights per last 14 days: A:4.5 (3.7), B:6.0 (4.4) Mean (SD) number of wet nights per 14 days at follow up: A:7.7 (3.9), B:7.3 (4.5) Side effects: B: rash (1)
Notes	Norwegian translation Direct comparison of imipramine and DDAVP Children comparable in terms of sex, age and weight No details of previous treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Janknegt 1990#

Methods	RCT (double-blind randomised crossover of dosages with placebo between) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned Follow up after 4 weeks
Participants	Number of children: 22 (18 boys) No dropouts Inclusion criteria: maximum of 4 dry nights a week during baseline Mean age: 10 years (range 6-16) Previous treatment: all used imipramine or other medications, or enuresis alarm (8), acupuncture (1), and psychotherapy (1) More than one method used with many patients Baseline wetting: mean (SD) number of dry nights per week: 1.3 (1.3)
Interventions	A: Placebo nasal pipette B: 20 µg desmopressin intranasally C: 40 µg desmopressin intranasally Duration of treatment: 1 month each condition
Outcomes	Mean (SD) number of dry nights per week: A:1.7 (1.8), B:3.6 (2.5), C:3.2 (2.2) At follow up mean (SD) number of dry nights per week: 2.2 (1.8) Morning urine osmolality not significantly different in pre-treatment or treatment periods Significant increase in body weight No significant changes in blood pressure, haematology or blood chemistry Side effects: most common adverse reactions were headaches (3) and stomach ache (3) (though no different from placebo)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Janknegt 1997

Methods	RCT (double blind multi-centre trial, method not given) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes 12 week open label follow up
Participants	Number of children: 65 (boys: A:18, B:19) 3 dropouts Exclusion criteria: diurnal wetting; other medical conditions; urological causes of wetting Mean age: 19.4 years (range 12-45) At least 6 wet nights in 2 weeks at baseline
Interventions	A (34): desmopressin tablets 200 µg B (31): desmopressin tablets 400 µg Duration of treatment: 4 weeks
Outcomes	Mean change from baseline wetting (wet nights per week 95% CI) A:-3.2 (-2.4, -4.1), B:-3.4 (-2.7, -4.1) Side effects: not mentioned
Notes	Only DDAVP responders Mixed age group (some adults)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kahan 1998

Methods	RCT (double-blind, method not specified) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned Follow up for 2 months
Participants	Number of children: 228 Dropouts: A 6, B 1; due to difficulty complying with schedule of behavioural therapy Inclusion criteria: primary nocturnal enuresis at least 2 times per week, age >7 years Exclusion criteria: previous treatment, other physical disorders, previous traumatic life events, psychiatric disorders, abnormal laboratory findings Baseline differences in wetting between groups: A 5.1 (SD 2.1); B 5.5 (1.8); C 5.8 (1.6): P=0.044
Interventions	A (70): desmopressin and behaviour therapy B (75): placebo and behaviour therapy C (76): desmopressin alone (20 µg intranasal) Duration 8 weeks
Outcomes	Wet nights at end of trial (N, mean, SD): A: 70, 3.0 (2.0); B: 75, 3.3 (2.2); C: 76, 4.5 (2.0) Number not achieving 14 dry nights: A: 48/70; B: 63/75; C: 45/76 Number failing or relapsing: A: 66/70; B: 69/75; 73/76 Wet nights after end of trial (N, mean, SD): A: 70, 2.6 (1.7); B: 74, 3.0 (2.0); C: 76, 4.7 (1.8) Side effects: nasal itch: A 5, B 1, C 4 7 dropouts due to problems with behavioural treatment schedule

Kahan 1998 *(Continued)*

Notes	Power calculation given Behaviour treatment = psychological (teaching self control, taking responsibility), bladder continence exercises, giving information about the mechanisms of wetting Blinding of treatment not possible due to differences in interventions (but placebo and DDAVP blinded) Group A had less wetting at baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kjoller 1984

Methods	RCT (double-blind) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned Follow up after 3 months
Participants	Number of children: 37 Dropouts from follow up: A:3, B:2 Inclusion criteria: normal, healthy children who had failed with previous treatment, informed consent, more than 25% wet nights during baseline Previous treatment: all failed treatment with tricyclic antidepressants and/or enuresis alarm Mean age: 11.0 years (range 9-15) Baseline wetting: mean (SD) number of wet nights per 100: A:56.6 (8.0), B:65.9 (7.5), C:64.7 (7.3)
Interventions	A (13): 10 µg DDAVP intranasally before bedtime B (12): 20 µg DDAVP intranasally before bedtime C (12): placebo Duration of treatment: 1 month
Outcomes	Number of wet nights per 100 (mean, SD): A:35.5 (10), B:35.0 (7.6), C:54.8 (8.8) Follow up: mean (SD) number of wet nights per 100: A:60.9 (11.4), B:60.0 (8.5), C:52.3 (8.9) Side effects: none reported DDAVP ineffective when participants had respiratory tract infections
Notes	Not reported if the groups were comparable

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lee 2005

Methods	RCT (randomly assigned to 1 of 3 groups) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: 53% also had daytime wetting but results available separately

Lee 2005 *(Continued)*

	Setting: 2 hospitals, 2003 to 2004
Participants	Number of children (boys): 145 (100) Monosymptomatic enuresis (Trial 1): 68 Polysymptomatic (+ daytime wetting, Trial 2): 77 Dropouts: 13 (drug side effects or outcome unknown: A: 3, B: 3, C: 7) Inclusion criteria: at least 3 wet nights/week Exclusion criteria: drug treatment in 14 days prior to start of study Age: 7.8 years (SD 2.5) (range 5 to 15) Baseline wetting: 6.36x/week (SD 1.5)
Interventions	Trial 1 (monosymptomatic enuresis) A (22): desmopressin 0.1 or 0.2 mg, oxybutynin 5 mg B (23): desmopressin0.2 mg increased to 0.4 mg if no response C (23): imipramine 25 mg Given orally before bedtime Duration of treatment: 6 months Follow up: none
Outcomes	Trial 1 Wet nights at 6 months, N mean (SD): A: 22, 0.93 (1.35), B: 23, 0.7 (0.95), C: 23, 2.0 (2.05) No. children cured (excellent response = 0-1 wet night per month): A: 14/22, B: 14/23, C: 3/23 No. children failed (not excellent): A: 8/22, B: 9/23, C: 20/23 Trial 2 Wet nights at 6 months, N mean (SD): A: 26, 1.2 (1.55), B: 26, 1.23 (0.88), C: 25, 2.63 (2) No. children cured (excellent response = 0-1 wet night per month): A: 9/26, B: 7/26, C: 3/25 No. children failed (not excellent): A: 17/26, B: 19/26, C: 22/25 Adverse effects (both trials, including dropouts): A: 0/51, B: 2/52, C: 22/55
Notes	Data obtained from author enabling results to be given separately for nocturia and daytime wetting groups Groups comparable at baseline on age, sex, disease type, baseline wetting Higher side effect and drop out rate in imipramine group

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Leebeek 2001

Methods	RCT (double blind parallel group study) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes Follow up at 2 weeks and 6 months after end of trial
Participants	Number of children (boys): 93 (62) Inclusion criteria: at least 6 wet nights per week Exclusion criteria: treatment in previous 2 weeks; daytime wetting/ pollakisuria; urological or psychological disease; poor motivation to use alarm Previous treatment: none in previous 2 weeks Age: 6-14 years Baseline wetting: mean number of wet nights: A: 6.14, B: 6.12 (NS)

Leebeek 2001 *(Continued)*

Interventions	A (47): alarm and desmopressin 40 µg intranasal for 3 weeks, then alarm and desmopressin 20 µg for 3 weeks, then alarm alone for 3 weeks B (46): alarm and placebo for 6 weeks, then alarm alone for 3 weeks
Outcomes	Wet nights (number, mean): First 3 weeks: A: 47, 2.93, B: 45, 3.86 (P=0.014) Last 3 weeks, alarm only: A: 43, 2.77, B: 39, 2.21 Number cured 2 weeks after end of trial: A: 15/47, B: 17/46 Number cured 6 months after end of trial: A: 17/47, B: 17/46 i.e. failed at 6 months: A: 20/47, B: 21/46 Wet nights at 6 months (number, mean): A: 41, 2.72, B: 37, 1.90 Adverse events: none in either group
Notes	Power calculation provided Groups comparable for sex and age SDs not given (authors contacted for more information) Study supported by drug company (Ferring Pharmaceuticals A/S Ferring)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Longstaffe 2000

Methods	RCT (computer generated randomisation) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes Setting: Recruited from hospital clinic and advertising
Participants	Number of children: 182 At 6 months 17 withdrew due to failure (A 8; B 5; C 4) Inclusion criteria: primary monosymptomatic nocturnal enuresis, age >7 years, wet >3 times per week, normal bladder capacity Exclusion criteria: daytime wetting, CNS disorder, developmental delay, current alarm or DDAVP treatment, encopresis, other medical problems
Interventions	A (61): alarm B (60): desmopressin intranasally C (61): placebo Duration 6 months, then failures crossed over to alternative arm for 6 months (not randomised)
Outcomes	Number not achieving 14 dry nights after 6 months: A: 26/61; B: 31/60; C: 38/61 All children improved psychologically, e.g. behaviour and self concept, regardless of outcome or treatment assignment Side effects: not mentioned
Notes	Dose of DDAVP not given No follow up as failures assigned to alternative treatment Blinding to method not possible for alarm group

Risk of bias

Bias	Authors' judgement	Support for judgement

Longstaffe 2000 *(Continued)*

Allocation concealment?	Low risk	A - Adequate

Martin 1993

Methods	RCT (double-blind randomised placebo controlled) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: No Only 7 DDAVP successes followed up
Participants	Number of children: 44 Boys: A:54%, B:41% Mean age (year): A:8.9, B:9.13 Previous treatment: all children had failed to improve during 1 month treatment with motivational therapy and bladder training Baseline wetting: mean (SD) % of dry nights per month: A:24.45 (18.8), B:19.9 (20)
Interventions	A (22): placebo B (22): 40 µg desmopressin drops 15 minutes before retiring Duration of treatment: 2 months
Outcomes	Mean (SD) % of dry nights per month after 2 months: A:47.4 (32.1), B:69.2 (33.5) Number (%) of children becoming totally dry: A:1 (5), B:5 (27) Side effects: anorexia (1)
Notes	Groups similar at baseline No follow up Very small sample Unclear about dropouts Inclusion/ exclusion criteria not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

Miller 1990a

Methods	RCT (multi-centre, double-blind) Trial A = Centre 1 Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned No significant differences between groups except that more older children in group (A) in one centre 4 weeks open label phase then 2 week no treatment Number at 2 week follow up: 1A:19, 1B:26, 1C:16
Participants	Number of children: 99 (70% boys) 4 dropouts Inclusion criteria: children aged 7-14 with nocturnal enuresis; informed consent from parents; 10 or more wet nights per fortnight; no organic urologic disorders; no urinary tract infection; no abnormal urine osmolality Previous treatment: 58% taken other drugs; 87% imipramine; 40% tried other measures of these, 76% tried enuresis alarm

Miller 1990a *(Continued)*

	Age range 7-14 (46% aged 7-8) Baseline wetting: mean number of wet nights in 14: 1A:12.3, 1B:11.8, 1C:12.3
Interventions	1A (32): 20 µg desmopressin acetate intranasally at bedtime 1B (36): 40 µg desmopressin acetate intranasally at bedtime 1C (31): placebo Duration of treatment: 4 weeks
Outcomes	Mean number of wet nights in final 14 days: 1A:8.7, 1B:7.0, 1C:10.7 Active treatment significantly different to placebo 2 week follow up: mean number of wet nights per 14: 1A:11.1, 1B:11.0, 1C:9.9 Side effects: no serious adverse events (6 minor)
Notes	No intention to treat Short follow up Statistics suggest sample size too small for conclusive findings No SDs

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Miller 1990b

Methods	RCT (multi-centre, double-blind) Trial B = Centre 2 Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned No significant differences between groups except that more older children in group (A) in one centre 4 weeks open label phase then 2 week no treatment Number at 2 week follow up: 2A:19, 2B:20, 2C:20
Participants	Number of children: 77 (70% boys) 4 dropouts Inclusion criteria: children aged 7-14 with nocturnal enuresis; informed consent from parents; 10 or more wet nights per fortnight; no organic urologic disorders; no urinary tract infection; no abnormal urine osmolality Previous treatment: 58% taken other drugs; 87% imipramine; 40% tried other measures of these, 76% tried enuresis alarm Age range 7-14 (46% aged 7-8) Baseline wetting: mean number of wet nights in 14: 2A:12.6, 2B:12.3, 2C:12.4
Interventions	2A (27): 20 µg desmopressin acetate intranasally at bedtime 2B (24): 40 µg desmopressin acetate intranasally at bedtime 2C (26): placebo Duration of treatment: 4 weeks
Outcomes	Mean number of wet nights in final 14 days: 2A:10.0, 2B:8.1, 2C:10.5 Active treatment significantly better than placebo except A versus C not significant 2 week follow up: mean number of wet nights per 14: 2A:10.8, 2B:11.4, 2C:11.3 Side effects: no serious adverse events (11 minor)
Notes	No intention to treat Short follow up Statistics suggest sample size too small for conclusive findings

Miller 1990b *(Continued)*

	No SDs

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Muller 2001#

Methods	RCT (double blind crossover, initial assignment of groups 'created at random') Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned
Participants	Number of children (boys): 40 (29) Inclusion criteria: at least 3 wet nights per week, primary nocturnal enuresis Exclusion criteria: anatomical abnormalities, abnormal serum or urine analysis Previous treatment: none Baseline wetting: mean wet nights 5.35 (median 5.5, 95% CI 4.5-6) Age (mean, median, range): A: 8.7, 8.9 (6-13); B: 8.6, 8 (6.3-11.9) Recruited from Children's Hospital, University of Kiel, Germany
Interventions	A (19): 20 µg desmopressin intranasally first 2 weeks B (21): 0.9% saline first 2 weeks Duration of treatment: crossed over after 2 weeks
Outcomes	Number of wet nights during trial, mean (median, 95% CI): A: 3.27 (3, 2 to 4); B: 4.9 (5.25, 4.5 to 6): (P<0.001) Responders to desmopressin (undefined): 27/40 children (67.5%). Data not provided for placebo treatment Reaction time: no difference between the groups Short-term memory: better on desmopressin, more words remembered, P=0.012 Children slept more deeply on desmopressin (14/18) than placebo (4/18), P=0.03
Notes	No useable data Groups comparable at baseline on gender, age, weight and height SDs not given (authors contacted for more infomation but not supplied)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Natochin 2000

Methods	CCT (randomisation using case record numbers) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes Setting: St Petersburg State Medical Academy, Russia
Participants	Number of children: 62 (43 boys) plus 22 (15) on placebo

Natochin 2000 *(Continued)*

	Inclusion criteria: primary nocturnal enuresis Exclusion criteria: other medication, daytime wetting, other disease Age: range 6-15 years (mean 9.8 +/- SD 7) Baseline wetting: at least 6 wet nights per 2 weeks
Interventions	A (32): desmopressin 10.5 - 24.5 µg intranasally B (30): diclofenac tablet 1 mg/kg body mass C (22): placebo (intranasally) for 2 weeks then given desmopressin Duration of treatment: A and B 4 weeks each, C (placebo) 2 weeks only Follow up: none
Outcomes	Number not achieving 14 dry nights: A: 11/32; B: 20/30; C: 21/22 Side effects: none reported
Notes	Extra information supplied by authors (method of randomisation, results confirmed, no side effects) Parallel groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Neveus 1999#

Methods	RCT (double blind crossover) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes
Participants	Number of children: 33 (30 boys) Dropouts: 2 extra withdrew Inclusion criteria: primary monosymptomatic nocturnal enuresis Previous treatment: resistant to 0.4 mg desmopressin Age: range 6-16 years, mean 10.4 Baseline wetting: at least 6 wet nights without treatment, mean 11.4 in 2 weeks
Interventions	A (33): 0.4 mg desmopressin orally B (33): 0.8 mg desmopressin orally C (33): placebo Duration: 5 nights each
Outcomes	Number not achieving 14 dry nights: A: 30/33; B: 27/33; C: 32/33 Side effects: not mentioned
Notes	Washout period of 48 hours between each phase No follow up as all children treated after end of trial with high dose desmopressin or combined desmopressin and anticholinergics

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Ng 2005

Methods	RCT 'randomly allocated' by consecutive sealed envelopes Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes
Participants	Number of children 105 Dropouts: 12 (defaulted from treatment: A7, B2, C3; defaulted from follow up A2, B2, C5) Inclusion: primary nocturnal enuresis Exclusion: UTI in previous 3 months, daytime wetting, polyuric disorders, abnormal urinalysis, renal disease, previous diuretics, unwilling to be randomised Previous treatment: none (excluded if had desmopressin, alarms or tricyclics) Age: range 7-12 years Baseline wetting: at least 3 wet nights in baseline 2 weeks
Interventions	A (35): alarm only ('Wet-Stop' alarm) B (38): oral desmopressing 200 µg, increased to 400 µg if > 1 wet night C (32): both treatments Duration of treatment: 12 weeks Follow up: 12 weeks
Outcomes	Wet nights during trial (N, mean (SD)): A: 28, 2.8 (2.2), B: 36, 2.6 (2.4), C: 29, 1.3 (1.9) Not achieving 14 dry nights: A: 27/35, B: 22/38, C: 12/32 (ITT, dropouts = failure) Wet nights after trial (N, mean (SD)): A: 24, 2.5 (2.4), B: 34, 3.4 (2.5), C: 24, 2.6 (2.7) Not achieving 14 dry nights or relapsing after: A: 35/35, B: 30/38, C: 19/32 (ITT, dropouts = failure) Adverse effects: none All children who responded completely to the alarm stayed dry afterwards
Notes	All children had star charts and kept wetting diaries Comparable at baseline on wetting frequency, age, gender, urine osmolality More children failed to comply in Group A (alarm only), these were included as failures in the dry night analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Post 1983a#

Methods	RCT (Trial 1 = multi-centre double-blind randomised crossover trial) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned Follow up after 1-3 months
Participants	Trial 1: Number of children: 52 (40 boys) Inclusion criteria: healthy children age 6-16; history of severe primary or secondary enuresis Exclusion criteria: organic causes Previous treatment: 18 had previous pharmacologic treatment; 3 had undergone urethral dilation procedures and 16 subjects had been involved in an identical study of lower dose (20 µg) of desmopressin Mean age (years): 9.0 Baseline wetting: mean (SEM) number of dry nights: 2.52 (0.28)

Post 1983a# *(Continued)*

Interventions	1A: 40 µg desmopressin intranasally at bedtime 1B: placebo Drinking prohibited until the next morning Duration of treatment: 2 weeks each arm
Outcomes	Trial 1 Mean (SEM) number of dry nights per 14: A:6.23 (0.65), B:4.00 (0.53) No significant order effects Post treatment results: mean number of dry nights per 14: 3.44 (0.50) Only 4 of 21 responders reported persistent effect During longer term study of 9 patients at Syracuse, the mean number of dry nights while taking desmopressin: 5.11 (1.31) was the same as that during the 2 week period: 5.11 (1.59) Side effects: not mentioned
Notes	Not stated if comparable groups No washout No details of dropouts - unclear if intention to treat Results from 3 centres combined because no significant difference in mean number of wet nights during active treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Post 1983b#

Methods	RCT (Trial 2 = multi-centre double-blind randomised crossover trial) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned Follow up after 1-3 months
Participants	Trial 2: Number of children: 20 (15 boys) Inclusion criteria: healthy children age 6-16; history of severe primary or secondary enuresis Exclusion criteria: organic causes Previous treatment: 18 had previous pharmacologic treatment; 3 had undergone urethral dilation procedures and 16 children had been involved in an identical study of lower dose (20 µg) of desmopressin Mean age: 8.9 years Baseline wetting: mean (SEM) number of dry nights: 1.90 (0.43)
Interventions	2A: 20 µg desmopressin intranasally at 8 pm each night 2B: placebo Drinking prohibited until the next morning Duration of treatment: 2 weeks each arm
Outcomes	Trial 2 Mean (SEM) number of dry nights per 14: A:4.25 (0.88), B:2.35 (0.51) Post treatment mean (SEM) number of dry nights per 14: 4.00 (0.66) Comparing the results of 16 children who had both low and high dose (Trial 1), they did better on high dose - mean paired increase (SEM): 2.18 (0.90), t=2.44 P=0.05. 6 children had increase of 3 or more dry nights while on higher dose Side effects: not mentioned
Notes	Not stated if comparable groups No washout

Post 1983b# *(Continued)*

	No details of dropouts - unclear if intention to treat Results from 3 centres combined because no significant difference in mean number of wet nights during active treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Radmayr 2001

Methods	RCT (details not given) Systematic baseline measure of wetting: Yes Organic causes excluded: No apart from UTI Daytime wetting excluded: Yes Setting: Recruitment from Department of Urology and Anaesthesiology, Austria Follow up 6 months after end of trial
Participants	Number of children (boys): 40 (31) Inclusion criteria: primary monosymptomatic nocturnal enuresis, high night-time urine production (polyuria), age >5 years Exclusion criteria: UTI Previous treatment: none Age mean (range): A: 8.6 (5-16), B: 8 (5-14) Baseline wetting 5.5 wet nights per week; mean (range): A: 5.5 (2-7), B: 6 (4-7)
Interventions	A (20): desmopressin, intranasal, 20 µg increasing to 40 µg if no response (12/20 children) B (20): laser acupuncture, see Notes Duration of treatment: 3 months
Outcomes	Response = decrease of 90% wet nights; partial response = decrease of 50%; failed = less than 50% decrease Non-response at end of trial: A: 3/20, B: 2/20 Partial response: A: 1/20, B: 4/20 Non-response at 6 months after end of trial: A: 3/20, B: 5/20 (counting 1 who did not finish acupuncture course as a failure) Partial response at 6 months: A:2/20, B:2/20 Adverse events: none in either group
Notes	Laser acupuncture described and illustrated, soft laser stimulation for 30 of several pre-defined acupuncture areas, 3 visits per week, minimum 10, maximum 15 visits

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Rittig 1988#

Methods	RCT (double-blind randomised crossover) Placebo period of 3 weeks randomly and blindly placed throughout treatment period Only patients who responded in dose titration period entered into randomised trial

Rittig 1988# *(Continued)*

	Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes 6 non-responders were not entered into crossover trial (all children, 4 girls and 2 boys)
Participants	Number of children: 34 (12 boys, 11 girls, 8 women and 3 men) Previous treatment: all failed previous treatments including alarms and/or tricyclics Age (years): children mean: 13 (range 8-17); adults mean: 25 (range 18-45) Baseline wetting: at least 3 wet nights per week
Interventions	Dose titration period then: A: optimum dose of desmopressin intranasally B: placebo (3 weeks blindly inserted into 24 week period) Duration of treatment: 24 weeks
Outcomes	Mean number of dry nights per week: A:7, B:4 Side effects: headache (2); sight disturbance (1)
Notes	Some adults Only patients who responded to desmopressin included Children and adults analysed together Placebo period not equal to active drug period No washout period No SDs

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Rodriguez 2001

Methods	RCT (method not specified) Systematic baseline measure of wetting: No Organic causes excluded: Yes Daytime wetting excluded: Yes
Participants	Number of children: 84 (80% boys) 3 dropouts after 3 months Inclusion criteria: wetting at least 1 time per week, age >7 years Exclusion criteria: diurnal enuresis, encopresis, neurological abnormalities Previous treatment: 38% of children Age range 7-14 years Hospital clinic, Spain
Interventions	A (30): bed alarm B (29): alarm and desmopressin 20 µg or 40 µg for more frequent wetters (>2 times per week) Duration 4-6 months
Outcomes	Response: A: 73.3%; B: 58.6% [=number not achieving 14 dry nights: A: 8/30; B: 12/29] All children treated with desmopressin if not cured at 6 months, therefore follow up not possible Side effects: not reported
Notes	Spanish language

Rodriguez 2001 *(Continued)*

	No follow up possible

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Rushton 1995

Methods	RCT (double-blind multi-institutional) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes Follow up after 5 months
Participants	Number of children: 96 (71 boys) No dropouts reported Inclusion criteria: confirmed monosymptomatic nocturnal enuresis; wet 6+ nights during 14 day baseline; no organic urological disease; no daytime wetting; no central diabetes insipidus; no urinary tract infection in previous 18 months; no use of any drug that could affect urine concentration; no medical treatment for hyperactivity or attention deficit disorder; no history of acute or perennial rhinitis, rhinorrhoea or nasal polyps; no clinically significant medical disease that may interfere with the study Mean age: 9.7 years (range 7-14) Severity: mean number of wet nights during 2 week baseline: A:11.16 (2.44), B:10.96 (2.53) No significant difference between the groups in demographics
Interventions	A (49): 20 µg desmopressin spray, dose doubled if not completely dry after 14 days B (47): placebo as above Duration of treatment: 4 weeks
Outcomes	Mean number of wet nights (SD) Period 1 (20 µg): A:7.91 (4.74), B:9.79 (3.28) Period 2 (40 µg): A:7.54 (5.04), B:9.79 (3.63) Side effects: none reported No meaningful differences between responders and non-responders with regard to demographic variables of age, gender, race or family history
Notes	No follow up results No details of previous treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Schulman 2001a

Methods	RCT (double-blind placebo controlled multi-centre parallel group design) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes Follow up: none

Schulman 2001a *(Continued)*

Participants	Number of children (boys): 193 (133) Dropouts: 6, due to non-compliance, consent withdrawn, failure to keep diary Inclusion criteria: at least 3 wet nights per week, informed consent Exclusion criteria: organic urological disease; daytime wetting; diabetes insipidus; UTI; known hypersensitivity to desmopressin; antibiotics, diuretics; hyperactivity Previous treatment: none in previous 30 days Age range 6-16 years Baseline wetting (mean in 2 weeks, range): A: 11 (5-14), B: 10 (4-14), C: 10 (6-14), D: 10 (6-14) Multicentre trial in 16 centres in USA
Interventions	A (46): desmopressin 0.2 mg oral B (49): desmopressin 0.4 mg C (50): desmopressin 0.6 mg D (48): matching placebo Treatment for 2 weeks, then 2-week placebo washout before being randomly assigned to second trial
Outcomes	Mean wet nights during 2 weeks treatment: A: 4 (SD 1.33), B: 3.5 (1.73), C: 3 (1.73), D: 4.5 (1.37) Number not achieving 14 dry nights during trial: A: 42/44, B: 42/48, C: 46/49, D: 47/47 Number improved during trial: A: 4, B: 9, C: 9, D: 3 Adverse events (1 or more per child): 43/143 on desmopressin, 13/48 on placebo. Headache, increased cough, and abdominal pain, all mild (81% desmopressin, 62% placebo) or otherwise moderate, all resolved before end of study and were mostly unrelated to treatment (79% desmopressin, 77% placebo) No child stopped trial because of side effects
Notes	First trial, dose ranging phase Fluid restriction 2 hours before bedtime Groups comparable at baseline Dropouts comparable from all groups No SDs - authors contacted for more information

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Schulman 2001b

Methods	RCT (double-blind placebo controlled multi-centre parallel group design) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes Follow up: none
Participants	Children from Trial 1 were eligible to be randomised again if they continued to have at least 3 wet nights per week during the placebo washout phase (31 children withdrew at this stage, 1 due to UTI) Dropouts: 11
Interventions	E (110): desmopressin 0.2 mg increased every 2 weeks if no response to max 0.6 mg F (38): matching placebo, tablets changed every 2 weeks if no response
Outcomes	Number of children requiring maximum increase in dose by 8 weeks: E: 86/99, F: 38/38 Improvement (50% reduction from baseline level of wetting): E: 51/99 [28 at 0.2 mg; 16 at 0.4 mg; 8 at 6 mg]: F: 7/35 First 2 weeks, desmopressin dose = 0.2 mg, mean wet nights in 1 week: E: n=109, mean=4 (SD 1.57), F: 38, 5 (1.54)

Schulman 2001b *(Continued)*

	Last 2 weeks, dose increased up to 0.6 mg: E: 99, 3.2 (1.69), F: 36, 4.5 (1.5) Adverse events (1 or more per child): 43/143 on desmopressin, 13/48 on placebo. Rhinitis, pharyngitis, infection, headache and fever, all mild (79% desmopressin, 92% placebo) or otherwise moderate, all resolved before end of study and were mostly unrelated to treatment (80% desmopressin, 83% placebo) 1 child on desmopressin and 1 on placebo stopped trial because of nervousness
Notes	Second trial, dose titration phase Fluid restriction 2 hours before bedtime Authors contacted for more information

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Segni 1982

Methods	RCT Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned Dropouts included in analysis Followed up after 1 week
Participants	Number of children: 40 (boys: A:14, B:10) Dropouts: A:0, B:12 Inclusion criteria: age 4-15 years; constant enuresis; no physical deformity or neurological damage Age 4-15 years with persistent enuresis, mean = 8.59 years Baseline wetting: A:5.2, B:4.6
Interventions	A (20): 20 to 30 µg desmopressin intranasally B (20): placebo Duration of treatment: 1 week
Outcomes	From graph: mean number of wet nights per week (SEM): A:2.2 (0.3), B:4.2 (0.4) No cases of total dryness Side effects: none reported
Notes	Italian language Not reported if comparable groups Comparison with placebo for 1 week only Results taken from graph Follow up for 1 week only No details of previous treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Sener 1998

Methods	RCT (method not specified) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned
Participants	Number of children: 85 Inclusion criteria: primary enuresis, age >5 years Exclusion criteria: enuresis treatment, other disease symptoms Age: mean 8 years, range 6-15 Baseline wetting at least 3 wet nights/week Dry nights in 2 weeks: A: 1.5 (SE 0.3); B: 1.5 (0.4); C: 1.1 (0.3)
Interventions	A (31): desmopressin 20 µg, intranasally B (29): indomethacin 100 mg/day, suppository C (25): placebo Duration of treatment: 4 weeks Follow up: none
Outcomes	DRY nights/2 weeks (number, mean, SE) on treatment: A: 31, 11.8 (0.5); B: 29, 8.9 (0.8); C: 25, 3.8 (0.8) [= WET nights per week, number, mean, SD: A: 31, 1.1 (SD 1.39); B: 29, 2.55 (2.15); C: 25, 5.1 (2)] Side effects: none reported
Notes	Parallel groups Blinding not possible due to different routes of administration

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Skoog 1997

Methods	RCT (parallel group trial) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes
Participants	Number of children: 147 (112 boys) 6 extra had no outcome data, 12/147 discontinued trial Inclusion criteria: Primary nocturnal enuresis Exclusion criteria: Organic urological disease, daytime wetting, diabetes insipidus, UTI, previous non-response to desmopressin Age: means 9.1 to 9.5 years, range 5-17 Baseline wetting at least 3 wet nights/week for 2 weeks 14 centres in USA
Interventions	A (37): 200 µg desmopressin orally B (35): 400 µg desmopressin C (37): 600 µg desmopressin D (38): placebo (double blind) Duration 6 weeks
Outcomes	Wet nights during last 2 weeks of trial (number, mean, SD): A: 33, 4 (SD 1.15), B: 33, 3.5 (1.44), C: 33, 3.5 (1.15), D: 36, 5 (1.2) Number not achieving 14 dry nights: A: 32/33, B: 29/33, C: 31/33, D: 36/36

Skoog 1997 *(Continued)*

	Side effects: 66 children on desmopressin and 21 on placebo had at least one adverse event (rhinitis, headache, pharyngitis, infection, cough) 92% were mild, 87% were unrelated to treatment, 89% resolved spontaneously. 3 serious events with desmopressin (2 vomiting, 1 atopic dermatitis) required treatment to stop
Notes	Dropouts and reasons clearly described No follow up Parallel group study (not crossover) Number of wet nights calculated from decrease from baseline, using SE at baseline as proxy

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Stenberg 1994#

Methods	RCT (double blind crossover) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes
Participants	Number of children: 10 Inclusion criteria: adolescents (puberty stage at least 2, at least 12 years) Exclusion criteria: treatment in previous 2 weeks, daytime wetting, UTI, urinary tract abnormalities Previous treatment: failed using alarms, desmopressin, other drugs Age range 11-21, median 13 years Baseline wetting 4.7 (SD 1.1) wet nights/week Department of Paediatric Surgery, Sweden
Interventions	A : desmopressin orally (dosage based on titration period) B : placebo Duration 4 weeks each
Outcomes	Wet nights during trial (number, mean, SD): A: 10, 1.8 (SD 1.4); B: 10, 4.1 (1.5) Side effects: headache (5); abdominal pain (6); nausea and vertigo (1) All resolved while treatment continued
Notes	No washout period

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Sukhai 1989#

Methods	RCT (double blind randomised crossover with 2 weeks washout) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes Follow up: 4 weeks to 6 months

Sukhai 1989# *(Continued)*

Participants	Number of children: 28 (21 boys) Inclusion criteria: Normal urine concentration capacity of 800 milliosmol/kg or higher; 3 or more wet nights per week during observation period; informed parental consent; no urological or renal disorder; no history of daytime wetting; no chronic urinary tract infection; no neurological or cardiovascular disease Previous treatment: 19 had previous attempts at treatment, including alarm (n=9) and tricyclic antidepressants (n=10) Age: mean 11 years (range 7 to 16) xx Severity at baseline: mean (SEM) number of dry nights per week = 1.4 (0.3) No dropouts
Interventions	A: enuresis alarm and bedtime dose of 20 µg DDAVP intranasally B: enuresis alarm and bedtime dose of placebo Duration of treatment: 2 weeks in each condition
Outcomes	Mean (SE) dry nights during treatment: A: 5.1 (0.4) B: 4.1 (0.4) 6 week follow up: 14 dry, 5 relapsed 4.5 month follow up: 9 remained dry Side effects: none reported Mean urine osmolality significantly increased from baseline Significantly higher urine osmolality with DDAVP than placebo Steady significant increase in body weight
Notes	Very good study

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Terho 1984#

Methods	RCT (double-blind, randomised crossover 2 periods of DDAVP and 2 periods on placebo, each period lasting 3 weeks and mutual order of all 4 periods being selected randomly) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes Follow up after 4 weeks
Participants	Number of children: 54 but 5 children excluded Exclusion criteria: faecal soiling; voiding difficulties; obvious neurological abnormalities; diurnal wetting Previous treatment: 49 had awakening protocol: 46 had water deprivation; 43 had tricyclic antidepressants; 13 had psychological counselling; 2 had alarm device and 1 had no previous treatment Age range: 7-16 years Baseline wetting: no details
Interventions	A: 20 µg DDAVP intranasal drops B: placebo Duration of treatment: 2 periods of 3 weeks in each condition
Outcomes	Mean % (SD) number of wet nights during combined periods: A:30.9 (28.7), B:57.5 (26.1) Only 1 child remained dry during follow up period Side effects: none reported

Terho 1984# *(Continued)*

Notes	Not reported if comparable groups No washout Unclear if intention to treat Baseline and follow up results lumped together 5 children excluded because of error in medication Short follow up

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Terho 1991#

Methods	RCT (double-blind randomised crossover) Children allocated to 2 periods of desmopressin and 2 periods of placebo. Each period lasted for 3 weeks and mutual order of all 4 periods selected at random. Closed by 3 week observation period Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes Follow up after 3 weeks
Participants	Number of children: 52 (35 boys), no dropouts Inclusion criteria: lifelong nocturnal enuresis; no diurnal wetting; no soiling; no urological or renal pathological conditions Previous treatment: 52 had night awakening; 52 had fluid restriction; 29 had used tricyclic antidepressants; 25 had used enuresis alarms Age range: 5-13 years Baseline wetting: mean (SD) number of dry nights per week: 0.6 (0.2)
Interventions	A: intranasal desmopressin (20 µg) at bedtime rising to 40 µg if no response B: placebo Duration of treatment: 2 periods of 3 weeks in each condition
Outcomes	Mean (SD) number of dry nights per week: Period 1: A:4.4, B:2.1 Period 2: A:4.6, B:2.5 15 children became totally dry during desmopressin treatment. 5 children remained dry after treatment. 47 patients relapsed after treatment Side effects: none reported
Notes	Not reported if comparable groups No washout reported Short follow up No SDs

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Tuvemo 1978#

Methods	RCT (double-blind randomised crossover) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned No follow up
Participants	Number of children: 18 Inclusion criteria: age at least 6 years Age: range 6-12 years Previous treatment: children had not responded satisfactorily to previous treatment with imipramine or amitriptyline Baseline wetting: mean (SEM) number of dry nights out of 28: 7.5 (2.98)
Interventions	A: 20 µg intranasal DDAVP (Minerin) just before bedtime after emptying bladder B: identical placebo as above Duration of treatment: 28 days in each condition
Outcomes	Mean (SE) number of dry nights out of 28: A:21.7 (1.72), B:12.1 (2.07) Side effects: none reported (no physical or subjective side effects observed) Number of children whose results were said to be excellent: 8; relatively good: 8; unsatisfactory: 2 Follow up after 6 months
Notes	Not stated if comparable groups No washout No details of dropouts: unclear if intention to treat No follow up Active and placebo results combined so cannot see any order or carryover effects

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Uygur 1997#

Methods	RCT (double-blind randomised crossover) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned
Participants	65 children but 11 excluded before RCT because they did not respond to trial of desmopressin Dropouts: 1 (UTI); 3 (found no longer to respond to desmopressin during 6 month open treatment) Inclusion criteria: primary nocturnal enuresis Exclusion criteria: urological disease, non-response to 2 week trial of desmopressin Age: 7-17 years Baseline wetting: '3 or more wet nights / week'
Interventions	A (54): desmopressin spray, 20 mcg or 40 mcg if no response B (54): placebo spray Duration of treatment: 2 weeks each arm Follow up: 6 months open desmopressin treatment
Outcomes	Wet nights in 2 weeks: A: 1, B: 9.6 (no SDs)

Uygur 1997# *(Continued)*

Notes	No useable data Population selected on the basis of all initially responding to desmopressin No SDs Baseline comparability of groups not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Vertucci 1997

Methods	RCT (double blind crossover) Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Not mentioned
Participants	Number of children: 57 Dropouts: 5 Inclusion criteria: primary nocturnal enuresis, age > 5 years, baseline wetting at least 3 nights/week, Previous treatment: not mentioned Age range 6-15 6 Child Neuropsychiatry Clinics, Italy
Interventions	A (29): desmopressin 30 µg intranasal then imipramine B (28): imipramine 0.9 mg/kg then desmopressin Duration of treatment: 3 weeks each Follow up: 2 weeks
Outcomes	Mean wet nights during first arm of trial: A: n=29, 1; B: 28, 2.5 Number not achieving 14 dry nights: A: 4/29; B: 9/28 Mean wet nights after both drugs: A: 29, 3.5; B: 28, 2.8 Side effects: desmopressin: 1 back pain, 1 inflamed nasal mucosa; imipramine: 1 pallor, restlessness and cold extremities
Notes	Data estimated from graphs Data only given from first arm of trial here No washout SDs not available Blinding not possible due to different routes of administration

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Wille 1986

Methods	RCT Systematic baseline measure of wetting: Yes Organic causes excluded: Yes Daytime wetting excluded: Yes

Wille 1986 *(Continued)*

	Distribution of social class of parents in 2 groups was similar Dropouts not included in analysis
Participants	Number of children: 50 (boys and girls) Inclusion criteria: age over 6 years; not dry for more than 6 months; at least 3 wet nights per week at baseline; written informed parental consent; no treatment for enuresis during previous year; no daytime wetting; no cardiovascular disease; no renal disorder; no neurological disease; no urinary tract infection Age: over 6 years Baseline wetting: mean number of dry nights per week: A:2.1, B:1.9 Number completing treatment: A:24, B:22
Interventions	A (25): intranasal desmopressin (20 µg) B (25): enuresis alarm Duration of treatment: 3 months
Outcomes	Mean (SEM) number of dry nights per week in first week: A:4.2 (0.5), B:2.5 (0.4) In last week of treatment: A:4.9 (0.5), B:6.3 (0.4) A:10 relapses given 3 months more treatment. Successful for 7/10 but 4/7 relapsed immediately and 1/7 after 2 months. B: 1 relapsed and further treatment unsuccessful. Side effects: A: nasal discomfort (5); bad taste in throat (2); B:false alarms (21); alarm did not go off (5); alarm did not wake child (15); other family members woken (15); child frightened by alarm (1). Lab tests: urine osmolality and density higher during treatment with desmopressin and urine osmolality in alarm group lower during treatment than before
Notes	Direct comparison of desmopressin and alarm Not intention to treat analysis Results taken from graph

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Yap 1998#

Methods	RCT (double blind crossover) Systematic baseline measure of wetting: Yes Organic causes excluded: No Daytime wetting excluded: Yes
Participants	Number of children: 37 (22 boys) 3 excluded because data incomplete Inclusion criteria: Primary monosymptomatic nocturnal enuresis Exclusion criteria: No current enuresis treatment Hospital clinic, Singapore
Interventions	A: (34) DDAVP 400 mg oral B (34) Placebo Duration of treatment 5 weeks, 2 week washout
Outcomes	Wet nights during trial (number, mean, SD): A: 34, 2.5 (2.7); B: 34, 4.5 (2.1) Number not achieving 14 dry nights: A: 11/34; B: 27/34 Wet nights after trial (number, mean, SD): 34, 4.5 (2.1)

Yap 1998# *(Continued)*

	Side effects: None reported (looked at body weight, BP, serum sodium and osmolality, urine osmolality, water retention or intoxication)
Notes	Groups comparable at baseline (same children) Follow up data unusable as all had had both treatments

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

= crossover trial; BP = blood pressure; CCT = controlled clinical trial; CI = confidence interval; CNS = central nervous system; DDAVP = 'brand name' for desmopressin; ITT = intention to treat; kg = kilograms; mg = milligrams; NS = not significant; RCT = randomised controlled trial; SD = standard deviation; SE = standard error; SEM = standard error of the mean; µg = micrograms; UTI = urinary tract infection; wt = weight

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bernasconi 1982	RCT: No Interventions: Desmopressin 5 µg, 10 µg rising to 40 µg
Bogaert 2005	RCT: Yes, of different doses of desmopressin Excluded as not actually used to treat enuresis (was a dose-response study for one day only) Intervention: single dose oral lyophilisate desmopressin: 30, 60, 120, 240, 360, 480 mg, placebo
Butler 2001	RCT: No Comparison group: No Intervention: Withdrawal from desmopressin or imipramine treatment, use of alarms optional
Caione 1994	RCT: No mention of method of allocation to groups Organic causes excluded: Yes Systematic baseline measures of wetting: Yes Interventions: Desmopressin, acupuncture
Caione 1995	RCT: Yes Participants all had daytime wetting as well as bedwetting; some adults were included Interventions: Desmopressin, oxybutynin
Capozza 1991	RCT: No Comparison group: Yes Organic causes excluded: Yes Systematic baseline measures of wetting: Yes Interventions: Desmopressin, acupuncture
Chiozza 1999	RCT: No (open multicentre trial) Comparison groups: Yes Interventions: desmopressin, 20, 30, 40 µg per day
Eckford 1994	RCT: Yes Comparison group: Yes Organic causes excluded: No Systematic baseline: No Systematic outcome measures: No Intervention: Desmopressin in adults with multiple sclerosis

Study	Reason for exclusion
Evans 1992	RCT: No Comparison group: Yes Organic causes excluded: Yes Systematic baseline measures of wetting: Yes Intervention: Intranasal desmopressin
Ferrie 1984	RCT: No Comparison group: crossover trial Organic causes excluded: Yes Systematic baseline measures of wetting: Yes Intervention: Intranasal desmopressin
Jones 1959	RCT: No Comparison group: Yes Organic causes excluded: No Systematic baseline measurement of wetting: No Systematic outcome measures: Yes Interventions: Pituitary snuff and propantheline
Key 1992	RCT: No Comparison group: No Organic causes excluded: Yes Systematic baseline: No Systematic outcome measures: Yes Intervention: Desmopressin (DDAVP)
Kim 2001	RCT: Yes Comparison group: Yes Organic causes excluded: No Systematic baseline measurement of wetting: Yes Systematic outcome measures: Yes (but improvement rates only) Interventions: Imipramine, desmopressin 2 children switched from imipramine to desmopressin due to side effects but data not given according to allocated groups therefore excluded as not intention to treat
Knudsen 1989	RCT: No Participants included adults (mean age 15.8 years) Intervention: Desmopressin
Marson 1955	RCT: Unclear Participants: 4 Intervention: pituitrin snuff, placebo snuff
Matthieson 1994	RCT: No Comparison group: No Organic causes excluded: Yes Systematic baseline: Yes Systematic outcome measures: Yes Intervention: Desmopressin
Miller 1988	RCT: No Comparison group: No Organic causes excluded: Yes Systematic baseline: No Systematic outcome measures: Yes Intervention: Desmopressin
Miller 1989	RCT: No

Study	Reason for exclusion
	Comparison group: No Organic causes excluded: Yes Systematic baseline: Yes Systematic outcome measures: Yes Intervention: Desmopressin
Monda 1995	RCT: No Comparison group: Yes Organic causes excluded: Yes Systematic baseline: No Systematic outcome measures: Yes Intervention: Desmopressin, imipramine, alarms
Petersen 1996	RCT: Yes Design: Randomized placebo-controlled, double blind, crossover study Participants were adults with multiple sclerosis, urinary frequency and incontinence Intervention: Desmopressin
Ramsden 1982	RCT: No Comparison group: Yes Organic causes excluded: Yes Systematic baseline: No Systematic outcome measures: Yes Intervention: Desmopressin (DDAVP)
Robinson 2002	RCT: Yes (double-blind randomised placebo controlled trial) Intervention: Desmopressin Excluded because participants were adult women with severe daytime incontinence
Snajderova 2001	RCT: No Intervention: Desmopressin
Steffens 1993	RCT: No Comparison group: No Organic causes excluded: Yes Systematic baseline: No Systematic outcome measures: No Intervention: Desmopressin (vasopressin)
Stenberg 1993	RCT: No Comparison group: No Organic causes excluded: No Systematic baseline: Yes Systematic outcome measures: Yes Intervention: Desmopressin
Stenberg 1995	RCT: No Comparison group: No Organic causes excluded: No Systematic baseline: Yes Systematic outcome measures: Yes Intervention: Desmopressin
Taylor 1981	RCT: Yes, crossover Participants: Adults with detrusor instability Intervention: Desmopressin (DDAVP)
Wood 1994	RCT: No

Study	Reason for exclusion
	Comparison group: Yes Organic causes excluded: No Systematic baseline: Yes Systematic outcome measures: Yes Intervention: Desmopressin

DDAVP = 'brand name' for desmopressin; µg = microgram; RCT = randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

Hjalmas 2001

Trial name or title	Cessation of desmopressin treatment after response
Methods	
Participants	77 responders to the SWEET trial
Interventions	Abrupt or tapered cessation of treatment after response to desmopressin
Outcomes	Relapse
Starting date	
Contact information	See references
Notes	

SWEET (Swedish Enuresis Trial)

DATA AND ANALYSES

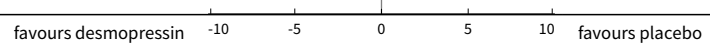
Comparison 1. DESMOPRESSIN VS PLACEBO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of wet nights per week during treatment	17		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 10 mcg vs placebo	2	57	Mean Difference (IV, Fixed, 95% CI)	-2.30 [-3.42, -1.18]
1.2 20 mcg vs placebo	12	813	Mean Difference (IV, Fixed, 95% CI)	-1.34 [-1.57, -1.11]
1.3 40 mcg vs placebo	6	424	Mean Difference (IV, Fixed, 95% CI)	-1.33 [-1.67, -0.99]
1.4 60 mcg vs placebo	2	164	Mean Difference (IV, Fixed, 95% CI)	-1.5 [-1.92, -1.08]

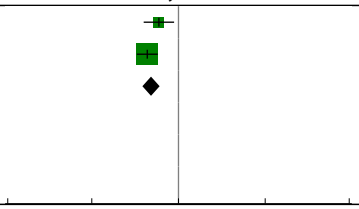
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 combined dose vs placebo	1	44	Mean Difference (IV, Fixed, 95% CI)	-3.4 [-4.71, -2.09]
1.6 dose titration vs placebo	2	231	Mean Difference (IV, Fixed, 95% CI)	-1.58 [-2.08, -1.09]
2 Number of wet nights per week during treatment (no SDs)			Other data	No numeric data
2.1 20 mcg vs placebo			Other data	No numeric data
2.2 dose titration vs placebo			Other data	No numeric data
3 Number failing to achieve 14 consecutive dry nights during treatment	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 10 mcg vs placebo	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.41, 0.98]
3.2 20 mcg vs placebo	5	288	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.78, 0.91]
3.3 40 mcg vs placebo	6	463	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.74, 0.89]
3.4 60 mcg vs placebo	2	165	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.88, 1.00]
3.5 80 mcg vs placebo	1	66	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.71, 1.00]
4 Number of wet nights per week at follow-up	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 10 mcg vs placebo	2	54	Mean Difference (IV, Fixed, 95% CI)	0.09 [-1.10, 1.27]
4.2 20 mcg vs placebo	1	22	Mean Difference (IV, Fixed, 95% CI)	0.54 [-1.15, 2.23]
5 Number of wet nights per week at followup (no SDs)			Other data	No numeric data
5.1 20 mcg vs placebo			Other data	No numeric data
5.2 40 mcg vs placebo			Other data	No numeric data
6 Number failing to achieve 14 consecutive dry nights or relapsing after cure	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.2 20 mcg vs placebo	1	34	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 DESMOPRESSIN VS PLACEBO, Outcome 1 Number of wet nights per week during treatment.

Study or subgroup	Desmopressin N	Desmopressin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.1.1 10 mcg vs placebo							
Aladjem 1982	15	1.5 (2.2)	17	4.4 (1.9)		62.07%	-2.88[-4.31,-1.45]
Kjoller 1984	13	2.5 (2.5)	12	3.8 (2.1)		37.93%	-1.35[-3.17,0.47]
Subtotal ***	**28**		**29**			**100%**	**-2.3[-3.42,-1.18]**
Heterogeneity: Tau²=0; Chi²=1.68, df=1(P=0.2); I²=40.36%							
Test for overall effect: Z=4.01(P<0.0001)							
1.1.2 20 mcg vs placebo							
Folwell 1997#	31	3.2 (2.5)	31	4.9 (2)		4.29%	-1.62[-2.74,-0.5]
Janknegt 1990#	22	3.4 (2.5)	22	5.3 (1.8)		3.24%	-1.9[-3.19,-0.61]
Kjoller 1984	12	2.5 (1.8)	12	3.8 (2.1)		2.12%	-1.39[-2.98,0.2]
Post 1983b#	20	4.9 (1.9)	20	5.8 (1.1)		5.61%	-0.9[-1.88,0.08]
Rushton 1995	49	4 (2.4)	47	4.9 (1.6)		8.14%	-0.94[-1.75,-0.13]
Schulman 2001a	44	4 (1.3)	47	4.5 (1.4)		17.45%	-0.5[-1.05,0.05]
Schulman 2001b	109	4 (1.6)	38	5 (1.5)		16.45%	-1[-1.57,-0.43]
Segni 1982	20	2.2 (1.3)	20	4.2 (1.8)		5.59%	-2[-2.98,-1.02]
Sener 1998	31	1.1 (1.4)	25	5.1 (2)		6.29%	-4[-4.92,-3.08]
Skoog 1997	33	4 (1.2)	36	5 (1.2)		17.46%	-1[-1.55,-0.45]
Terho 1984#	54	2.2 (2)	54	4 (1.8)		10.27%	-1.86[-2.58,-1.14]
Tuvemo 1978#	18	1.6 (1.8)	18	4 (2.2)		3.09%	-2.37[-3.69,-1.05]
Subtotal ***	**443**		**370**			**100%**	**-1.34[-1.57,-1.11]**
Heterogeneity: Tau²=0; Chi²=52.18, df=11(P<0.0001); I²=78.92%							
Test for overall effect: Z=11.35(P<0.0001)							
1.1.3 40 mcg vs placebo							
Janknegt 1990#	22	3.8 (2.2)	22	5.3 (1.8)		8.25%	-1.5[-2.69,-0.31]
Martin 1993	22	2.2 (2.3)	22	3.7 (2.3)		6.58%	-1.52[-2.85,-0.19]
Post 1983a#	52	3.9 (2.3)	52	5 (1.9)		17.27%	-1.1[-1.92,-0.28]
Schulman 2001a	48	3.5 (1.7)	47	4.5 (1.4)		29.62%	-1[-1.63,-0.37]
Skoog 1997	33	3.5 (1.4)	36	5 (1.2)		29.47%	-1.5[-2.13,-0.87]
Yap 1998#	34	2.5 (2.7)	34	4.5 (2.1)		8.81%	-2[-3.15,-0.85]
Subtotal ***	**211**		**213**			**100%**	**-1.33[-1.67,-0.99]**
Heterogeneity: Tau²=0; Chi²=3.11, df=5(P=0.68); I²=0%							
Test for overall effect: Z=7.63(P<0.0001)							
1.1.4 60 mcg vs placebo							
Schulman 2001a	48	3 (1.7)	47	4.5 (1.4)		43.91%	-1.5[-2.13,-0.87]
Skoog 1997	33	3.5 (1.2)	36	5 (1.2)		56.09%	-1.5[-2.05,-0.95]
Subtotal ***	**81**		**83**			**100%**	**-1.5[-1.92,-1.08]**
Heterogeneity: Tau²=0; Chi²=0, df=1(P=1); I²=0%							
Test for overall effect: Z=7.08(P<0.0001)							
1.1.5 combined dose vs placebo							
Birkasova 1978#	22	2.1 (2.3)	22	5.5 (2.2)		100%	-3.4[-4.71,-2.09]
Subtotal ***	**22**		**22**			**100%**	**-3.4[-4.71,-2.09]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.07(P<0.0001)							
1.1.6 dose titration vs placebo							



Study or subgroup	Desmopressin N	Desmopressin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Rushton 1995	49	3.8 (2.5)	47	4.9 (1.8)		32.13%	-1.13[-2.01,-0.25]
Schulman 2001b	99	3.2 (1.7)	36	5 (1.5)		67.87%	-1.8[-2.4,-1.2]
Subtotal ***	**148**		**83**			**100%**	**-1.58[-2.08,-1.09]**
Heterogeneity: Tau^2=0; Chi^2=1.52, df=1(P=0.22); I^2=34.33%							
Test for overall effect: Z=6.25(P<0.0001)							
Test for subgroup differences: Chi^2=12.29, df=1 (P=0.03), I^2=59.33%							

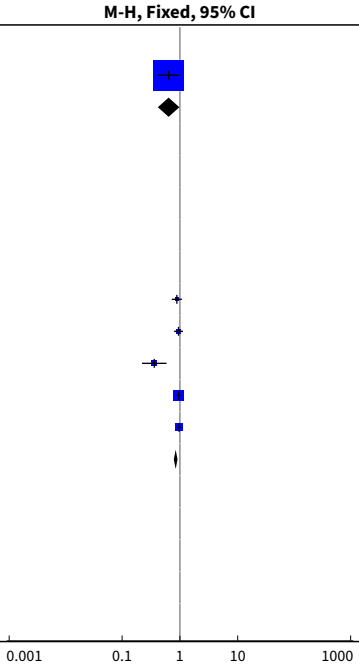


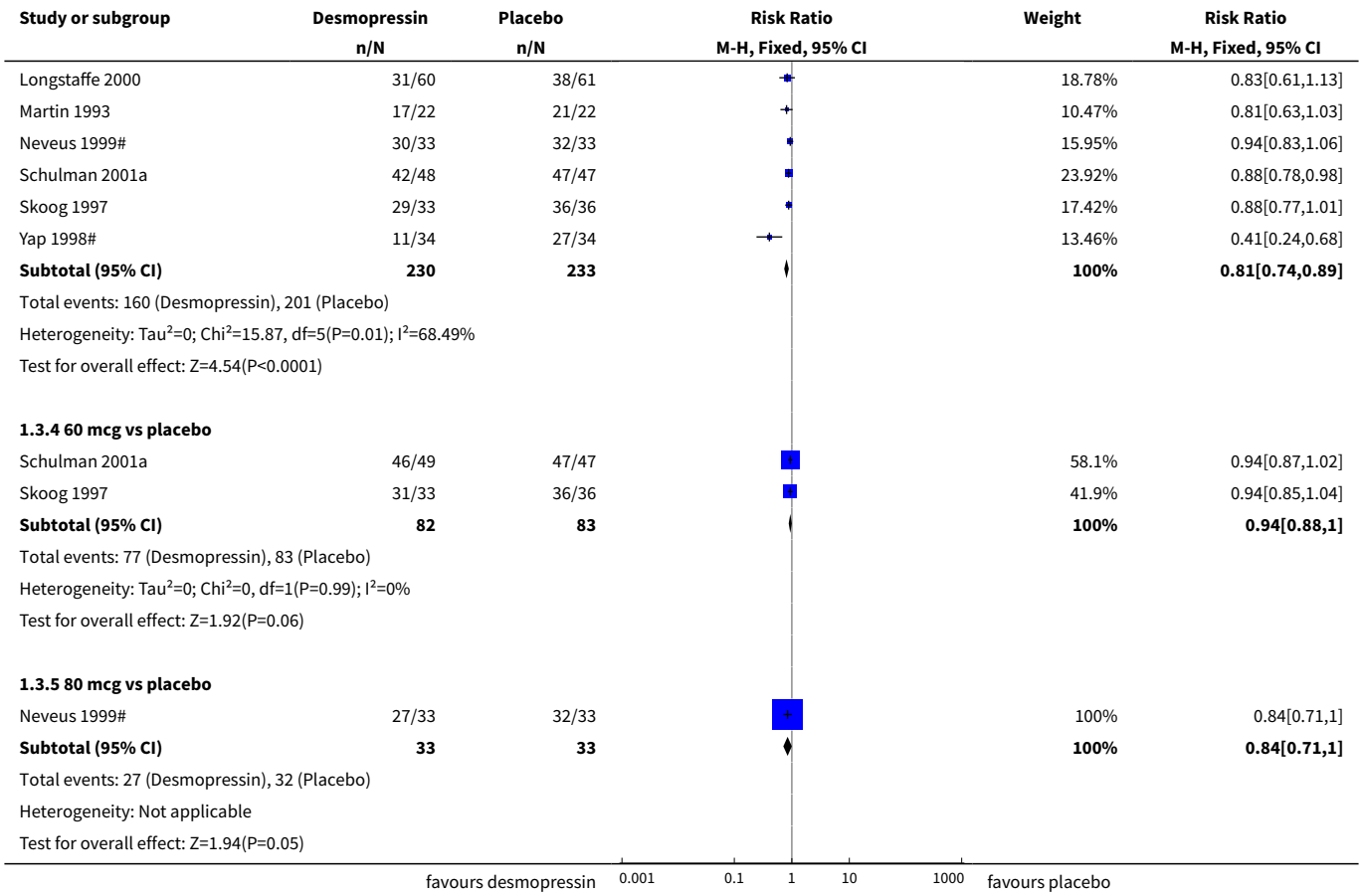
Analysis 1.2. Comparison 1 DESMOPRESSIN VS PLACEBO, Outcome 2 Number of wet nights per week during treatment (no SDs).

Study	Number of wet nights per week during treatment (no SDs) Desmopressin	Placebo
20 mcg vs placebo		
Dimson 1986#	3.4 wet nights, n=17	5.0 wet nights, n=17
Fjellestad 1987#	2.9 wet nights, n=19	4.5 wet nights, n=19
Miller 1990a	4.4 wet nights, n=19	5.4 wet nights, n=31
Miller 1990b	5 wet nights, n=27	5.3 wet nights, n=26
Muller 2001#	3.27 wet nights, n=19	4.9 wet nights, n=21
dose titration vs placebo		
Rittig 1988#	0 wet nights, n=34	3 wet nights, n=34
Terho 1991#	2.3 wet nights, n=52	4.7 wet nights, n=52
Uygur 1997#	0.5 wet nights, n=54	4.8 wet nights, n=54

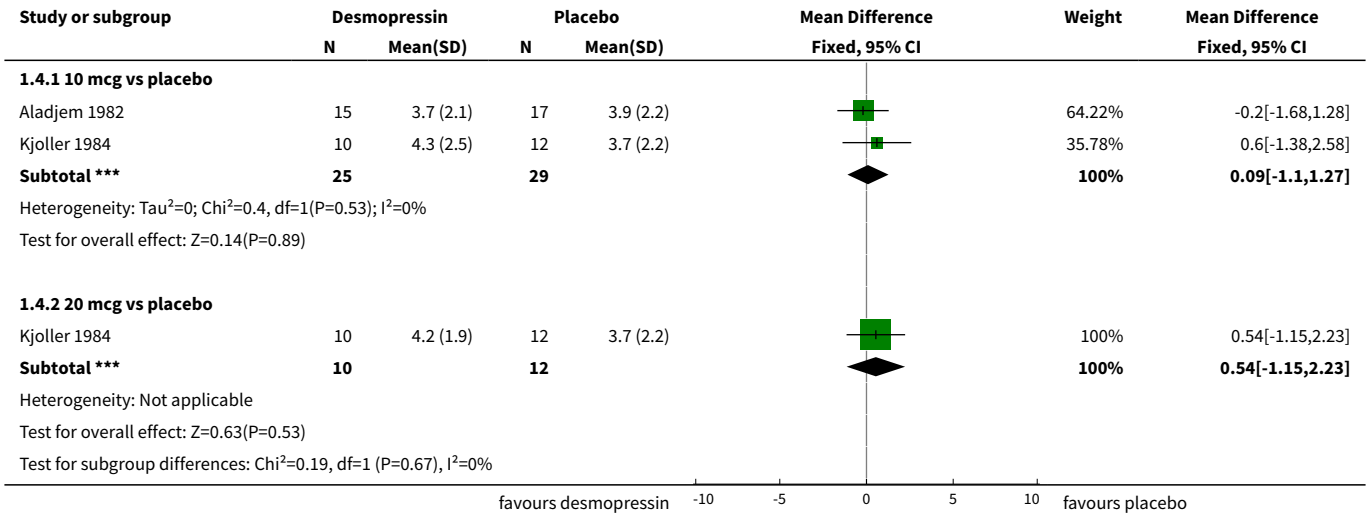
Analysis 1.3. Comparison 1 DESMOPRESSIN VS PLACEBO, Outcome 3 Number failing to achieve 14 consecutive dry nights during treatment.

Study or subgroup	Desmopressin n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 10 mcg vs placebo					
Aladjem 1982	9/15	16/17		100%	0.64[0.41,0.98]
Subtotal (95% CI)	**15**	**17**		**100%**	**0.64[0.41,0.98]**
Total events: 9 (Desmopressin), 16 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.05(P=0.04)					
1.3.2 20 mcg vs placebo					
Dimson 1986#	15/17	17/17		12.3%	0.89[0.72,1.08]
Fjellestad 1987#	18/20	19/20		13.35%	0.95[0.79,1.13]
Natochin 2000	11/32	21/22		17.49%	0.36[0.22,0.59]
Schulman 2001a	42/44	47/47		32.3%	0.95[0.88,1.03]
Skoog 1997	32/33	36/36		24.56%	0.97[0.89,1.05]
Subtotal (95% CI)	**146**	**142**		**100%**	**0.84[0.78,0.91]**
Total events: 118 (Desmopressin), 140 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=34.26, df=4(P<0.0001); I^2=88.33%					
Test for overall effect: Z=4.45(P<0.0001)					
1.3.3 40 mcg vs placebo					





Analysis 1.4. Comparison 1 DESMOPRESSIN VS PLACEBO, Outcome 4 Number of wet nights per week at follow-up.



Analysis 1.5. Comparison 1 DESMOPRESSIN VS PLACEBO, Outcome 5 Number of wet nights per week at followup (no SDs).

Study	Number of wet nights per week at followup (no SDs) Desmopressin	Placebo
20 mcg vs placebo		
Miller 1990a	5.6 wet nights, n=19	4.9 wet nights, n=16
Miller 1990b	5.4 wet nights, n=19	5.7 wet nights, n=20
40 mcg vs placebo		
Miller 1990a	5.5 wet nights, n=26	4.9 wet nights, n=16
Miller 1990b	5.7 wet nights, n=20	5.7 wet nights, n=20

Analysis 1.6. Comparison 1 DESMOPRESSIN VS PLACEBO, Outcome 6 Number failing to achieve 14 consecutive dry nights or relapsing after cure.

Study or subgroup	Desmopressin n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.2 20 mcg vs placebo					
Dimson 1986#	17/17	17/17			Not estimable
Subtotal (95% CI)	**17**	**17**			**Not estimable**
Total events: 17 (Desmopressin), 17 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

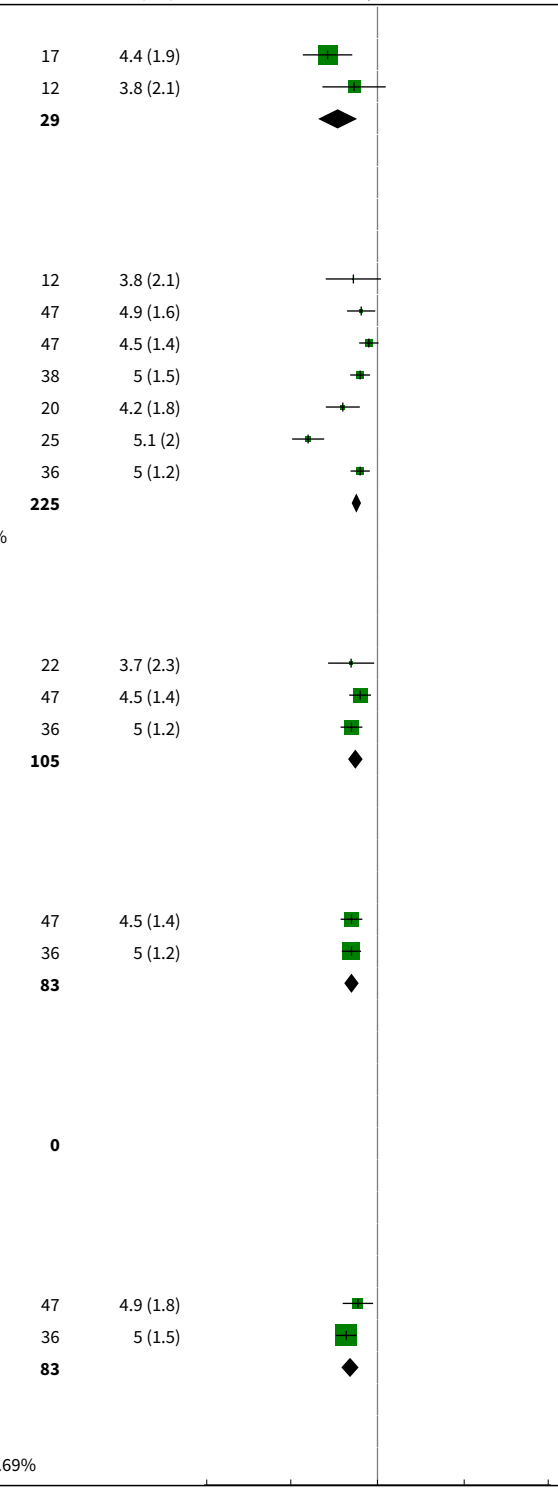
Comparison 2. DESMOPRESSIN VS PLACEBO excluding crossover trials

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of wet nights per week during treatment	9		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 10 mcg vs placebo	2	57	Mean Difference (IV, Fixed, 95% CI)	-2.30 [-3.42, -1.18]
1.2 20 mcg vs placebo	7	523	Mean Difference (IV, Fixed, 95% CI)	-1.22 [-1.49, -0.95]
1.3 40 mcg vs placebo	3	208	Mean Difference (IV, Fixed, 95% CI)	-1.28 [-1.70, -0.86]
1.4 60 mcg vs placebo	2	164	Mean Difference (IV, Fixed, 95% CI)	-1.5 [-1.92, -1.08]
1.5 combined dose vs placebo	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.6 dose titration vs placebo	2	231	Mean Difference (IV, Fixed, 95% CI)	-1.58 [-2.08, -1.09]
2 Number of wet nights per week during treatment (no SDs)			Other data	No numeric data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 20 mcg vs placebo			Other data	No numeric data
2.2 dose titration vs placebo			Other data	No numeric data
3 Number failing to achieve 14 consecutive dry nights during treatment	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 10 mcg vs placebo	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.41, 0.98]
3.2 20 mcg vs placebo	3	214	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.75, 0.90]
3.3 40 mcg vs placebo	4	329	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.77, 0.95]
3.4 60 mcg vs placebo	2	165	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.88, 1.00]
4 Number of wet nights per week at follow-up	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 10 mcg vs placebo	2	54	Mean Difference (IV, Fixed, 95% CI)	0.09 [-1.10, 1.27]
4.2 20 mcg vs placebo	1	22	Mean Difference (IV, Fixed, 95% CI)	0.54 [-1.15, 2.23]
5 Number of wet nights per week at followup (no SDs)			Other data	No numeric data
5.1 20 mcg vs placebo			Other data	No numeric data
5.2 40 mcg vs placebo			Other data	No numeric data
6 Number failing to achieve 14 consecutive dry nights or relapsing after cure	0		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 10 mcg vs placebo	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 20 mcg vs placebo	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 40 mcg vs placebo	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.4 60 mcg vs placebo	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.5 80 mcg vs placebo	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 DESMOPRESSIN VS PLACEBO excluding crossover trials, Outcome 1 Number of wet nights per week during treatment.

Study or subgroup	Desmopressin N	Desmopressin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.1.1 10 mcg vs placebo							
Aladjem 1982	15	1.5 (2.2)	17	4.4 (1.9)		62.07%	-2.88[-4.31,-1.45]
Kjoller 1984	13	2.5 (2.5)	12	3.8 (2.1)		37.93%	-1.35[-3.17,0.47]
Subtotal ***	**28**		**29**			**100%**	**-2.3[-3.42,-1.18]**
Heterogeneity: Tau^2=0; Chi^2=1.68, df=1(P=0.2); I^2=40.36%							
Test for overall effect: Z=4.01(P<0.0001)							
2.1.2 20 mcg vs placebo							
Kjoller 1984	12	2.5 (1.8)	12	3.8 (2.1)		2.88%	-1.39[-2.98,0.2]
Rushton 1995	49	4 (2.4)	47	4.9 (1.6)		11.07%	-0.94[-1.75,-0.13]
Schulman 2001a	44	4 (1.3)	47	4.5 (1.4)		23.74%	-0.5[-1.05,0.05]
Schulman 2001b	109	4 (1.6)	38	5 (1.5)		22.38%	-1[-1.57,-0.43]
Segni 1982	20	2.2 (1.3)	20	4.2 (1.8)		7.61%	-2[-2.98,-1.02]
Sener 1998	31	1.1 (1.4)	25	5.1 (2)		8.56%	-4[-4.92,-3.08]
Skoog 1997	33	4 (1.2)	36	5 (1.2)		23.76%	-1[-1.55,-0.45]
Subtotal ***	**298**		**225**			**100%**	**-1.22[-1.49,-0.95]**
Heterogeneity: Tau^2=0; Chi^2=45.34, df=6(P<0.0001); I^2=86.77%							
Test for overall effect: Z=8.84(P<0.0001)							
2.1.3 40 mcg vs placebo							
Martin 1993	22	2.2 (2.3)	22	3.7 (2.3)		10.03%	-1.52[-2.85,-0.19]
Schulman 2001a	48	3.5 (1.7)	47	4.5 (1.4)		45.11%	-1[-1.63,-0.37]
Skoog 1997	33	3.5 (1.4)	36	5 (1.2)		44.87%	-1.5[-2.13,-0.87]
Subtotal ***	**103**		**105**			**100%**	**-1.28[-1.7,-0.86]**
Heterogeneity: Tau^2=0; Chi^2=1.36, df=2(P=0.51); I^2=0%							
Test for overall effect: Z=5.94(P<0.0001)							
2.1.4 60 mcg vs placebo							
Schulman 2001a	48	3 (1.7)	47	4.5 (1.4)		43.91%	-1.5[-2.13,-0.87]
Skoog 1997	33	3.5 (1.2)	36	5 (1.2)		56.09%	-1.5[-2.05,-0.95]
Subtotal ***	**81**		**83**			**100%**	**-1.5[-1.92,-1.08]**
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%							
Test for overall effect: Z=7.08(P<0.0001)							
2.1.5 combined dose vs placebo							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.1.6 dose titration vs placebo							
Rushton 1995	49	3.8 (2.5)	47	4.9 (1.8)		32.13%	-1.13[-2.01,-0.25]
Schulman 2001b	99	3.2 (1.7)	36	5 (1.5)		67.87%	-1.8[-2.4,-1.2]
Subtotal ***	**148**		**83**			**100%**	**-1.58[-2.08,-1.09]**
Heterogeneity: Tau^2=0; Chi^2=1.52, df=1(P=0.22); I^2=34.33%							
Test for overall effect: Z=6.25(P<0.0001)							
Test for subgroup differences: Chi^2=5.11, df=1 (P=0.28), I^2=21.69%							

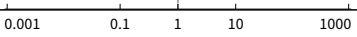


Analysis 2.2. Comparison 2 DESMOPRESSIN VS PLACEBO excluding crossover trials, Outcome 2 Number of wet nights per week during treatment (no SDs).

Study	Number of wet nights per week during treatment (no SDs) Desmopressin	Placebo
20 mcg vs placebo		
Miller 1990a	4.4 wet nights, n=19	5.4 wet nights, n=31
Miller 1990b	5 wet nights, n=27	5.3 wet nights, n=26

Analysis 2.3. Comparison 2 DESMOPRESSIN VS PLACEBO excluding crossover trials, Outcome 3 Number failing to achieve 14 consecutive dry nights during treatment.

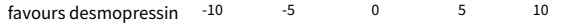
Study or subgroup	Desmopressin n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.3.1 10 mcg vs placebo					
Aladjem 1982	9/15	16/17		100%	0.64[0.41,0.98]
Subtotal (95% CI)	**15**	**17**		**100%**	**0.64[0.41,0.98]**
Total events: 9 (Desmopressin), 16 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.05(P=0.04)					
2.3.2 20 mcg vs placebo					
Natochin 2000	11/32	21/22		23.52%	0.36[0.22,0.59]
Schulman 2001a	42/44	47/47		43.44%	0.95[0.88,1.03]
Skoog 1997	32/33	36/36		33.04%	0.97[0.89,1.05]
Subtotal (95% CI)	**109**	**105**		**100%**	**0.82[0.75,0.9]**
Total events: 85 (Desmopressin), 104 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=42.43, df=2(P<0.0001); I^2=95.29%					
Test for overall effect: Z=4.39(P<0.0001)					
2.3.3 40 mcg vs placebo					
Longstaffe 2000	31/60	38/61		26.61%	0.83[0.61,1.13]
Martin 1993	17/22	21/22		14.83%	0.81[0.63,1.03]
Schulman 2001a	42/48	47/47		33.88%	0.88[0.78,0.98]
Skoog 1997	29/33	36/36		24.68%	0.88[0.77,1.01]
Subtotal (95% CI)	**163**	**166**		**100%**	**0.85[0.77,0.95]**
Total events: 119 (Desmopressin), 142 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.58, df=3(P=0.9); I^2=0%					
Test for overall effect: Z=2.98(P=0)					
2.3.4 60 mcg vs placebo					
Schulman 2001a	46/49	47/47		58.1%	0.94[0.87,1.02]
Skoog 1997	31/33	36/36		41.9%	0.94[0.85,1.04]
Subtotal (95% CI)	**82**	**83**		**100%**	**0.94[0.88,1]**
Total events: 77 (Desmopressin), 83 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=1.92(P=0.06)					



favours desmopressin favours placebo

Analysis 2.4. Comparison 2 DESMOPRESSIN VS PLACEBO excluding crossover trials, Outcome 4 Number of wet nights per week at follow-up.

Study or subgroup	Desmopressin N	Desmopressin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.4.1 10 mcg vs placebo							
Aladjem 1982	15	3.7 (2.1)	17	3.9 (2.2)		64.22%	-0.2[-1.68,1.28]
Kjoller 1984	10	4.3 (2.5)	12	3.7 (2.2)		35.78%	0.6[-1.38,2.58]
Subtotal ***	**25**		**29**			**100%**	**0.09[-1.1,1.27]**
Heterogeneity: Tau^2=0; Chi^2=0.4, df=1(P=0.53); I^2=0%							
Test for overall effect: Z=0.14(P=0.89)							
2.4.2 20 mcg vs placebo							
Kjoller 1984	10	4.2 (1.9)	12	3.7 (2.2)		100%	0.54[-1.15,2.23]
Subtotal ***	**10**		**12**			**100%**	**0.54[-1.15,2.23]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.63(P=0.53)							
Test for subgroup differences: Chi^2=0.19, df=1 (P=0.67), I^2=0%							



Analysis 2.5. Comparison 2 DESMOPRESSIN VS PLACEBO excluding crossover trials, Outcome 5 Number of wet nights per week at followup (no SDs).

Study	Number of wet nights per week at followup (no SDs) Desmopressin	Placebo
	20 mcg vs placebo	
Miller 1990a	5.6 wet nights, n=19	4.9 wet nights, n=16
Miller 1990b	5.4 wet nights, n=19	5.7 wet nights, n=20
	40 mcg vs placebo	
Miller 1990a	5.5 wet nights, n=26	4.9 wet nights, n=16
Miller 1990b	5.7 wet nights, n=20	5.7 wet nights, n=20

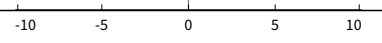
Comparison 3. DESMOPRESSIN: COMPARING DOSES

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of wet nights per week during treatment	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 10 vs 20 mcg	1	25	Mean Difference (IV, Fixed, 95% CI)	0.0 [-1.72, 1.72]
1.2 20 vs 40 mcg	3	202	Mean Difference (IV, Fixed, 95% CI)	0.42 [-0.01, 0.84]
1.3 20 vs 60 mcg	2	158	Mean Difference (IV, Fixed, 95% CI)	0.72 [0.30, 1.14]
1.4 40 vs 60 mcg	2	162	Mean Difference (IV, Fixed, 95% CI)	0.23 [-0.24, 0.69]

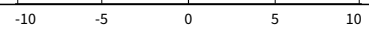
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Number of wet nights per week during treatment (no SDs)			Other data	No numeric data
2.1 20 mcg vs 40 mcg			Other data	No numeric data
3 Number failing to achieve 14 consecutive dry nights during treatment	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 20 mcg vs 40 mcg	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 20 mcg vs 60 mcg	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 40 mcg vs 60 mcg	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 40 mcg vs 80 mcg	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Number of wet nights per week at follow-up	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 10 vs 20 mcg	1	20	Mean Difference (IV, Fixed, 95% CI)	0.10 [-1.85, 2.05]
5 Number of wet nights per week at followup (no SDs)			Other data	No numeric data
5.1 20 mcg vs 40 mcg			Other data	No numeric data

Analysis 3.1. Comparison 3 DESMOPRESSIN: COMPARING DOSES, Outcome 1 Number of wet nights per week during treatment.

Study or subgroup	Low dose N	Low dose Mean(SD)	High dose N	High dose Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.1.1 10 vs 20 mcg							
Kjoller 1984	13	2.5 (2.5)	12	2.5 (1.8)		100%	0[-1.72,1.72]
Subtotal ***	**13**		**12**			**100%**	**0[-1.72,1.72]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.1.2 20 vs 40 mcg							
Janknegt 1990#	22	3.4 (2.5)	22	3.8 (2.2)		9.25%	-0.4[-1.79,0.99]
Schulman 2001a	44	4 (1.3)	48	3.5 (1.7)		45.46%	0.5[-0.13,1.13]
Skoog 1997	33	4 (1.2)	33	3.5 (1.4)		45.3%	0.5[-0.13,1.13]
Subtotal ***	**99**		**103**			**100%**	**0.42[-0.01,0.84]**
Heterogeneity: $Tau^2=0$; $Chi^2=1.46$, df=2(P=0.48); $I^2=0\%$							
Test for overall effect: Z=1.93(P=0.05)							
3.1.3 20 vs 60 mcg							
Schulman 2001a	44	4 (1.3)	48	3 (1.7)		43.87%	1[0.37,1.63]
Skoog 1997	33	4 (1.2)	33	3.5 (1.2)		56.13%	0.5[-0.05,1.05]



Study or subgroup	Low dose N	Low dose Mean(SD)	High dose N	High dose Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Subtotal ***	**77**		**81**			**100%**	**0.72[0.3,1.14]**
Heterogeneity: Tau²=0; Chi²=1.37, df=1(P=0.24); I²=26.92%							
Test for overall effect: Z=3.39(P=0)							
3.1.4 40 vs 60 mcg							
Schulman 2001a	48	3.5 (1.7)	48	3 (1.7)		45.21%	0.5[-0.19,1.19]
Skoog 1997	33	3.5 (1.4)	33	3.5 (1.2)		54.79%	0[-0.63,0.63]
Subtotal ***	**81**		**81**			**100%**	**0.23[-0.24,0.69]**
Heterogeneity: Tau²=0; Chi²=1.1, df=1(P=0.29); I²=8.95%							
Test for overall effect: Z=0.95(P=0.34)							
Test for subgroup differences: Chi²=2.78, df=1 (P=0.43), I²=0%							

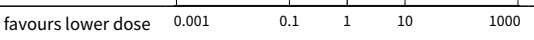


Analysis 3.2. Comparison 3 DESMOPRESSIN: COMPARING DOSES, Outcome 2 Number of wet nights per week during treatment (no SDs).

Study	Number of wet nights per week during treatment (no SDs) lower dose	higher dose
20 mcg vs 40 mcg		
Miller 1990a	4.4 wet nights, n=19	3.5 wet nights, n=26
Miller 1990b	5 wet nights, n=27	4 wet nights, n=24

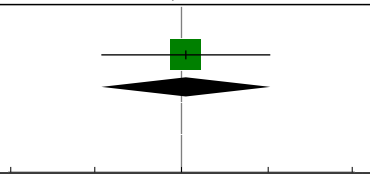
Analysis 3.3. Comparison 3 DESMOPRESSIN: COMPARING DOSES, Outcome 3 Number failing to achieve 14 consecutive dry nights during treatment.

Study or subgroup	lower dose n/N	higher dose n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
3.3.1 20 mcg vs 40 mcg				
Schulman 2001a	42/44	42/48		1.09[0.96,1.24]
Skoog 1997	32/33	29/33		1.1[0.96,1.27]
3.3.2 20 mcg vs 60 mcg				
Schulman 2001a	42/44	46/49		1.02[0.92,1.12]
Skoog 1997	32/33	31/33		1.03[0.93,1.15]
3.3.3 40 mcg vs 60 mcg				
Schulman 2001a	42/48	46/49		0.93[0.82,1.06]
Skoog 1997	29/33	31/33		0.94[0.8,1.09]
3.3.4 40 mcg vs 80 mcg				
Neveus 1999#	30/33	27/33		1.11[0.92,1.35]



Analysis 3.4. Comparison 3 DESMOPRESSIN: COMPARING DOSES, Outcome 4 Number of wet nights per week at follow-up.

Study or subgroup	Low dose N	Low dose Mean(SD)	High dose N	High dose Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.4.1 10 vs 20 mcg							
Kjoller 1984	10	4.3 (2.5)	10	4.2 (1.9)		100%	0.1[-1.85,2.05]
Subtotal ***	**10**		**10**			**100%**	**0.1[-1.85,2.05]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.1(P=0.92)							



low dose better — high dose better

Analysis 3.5. Comparison 3 DESMOPRESSIN: COMPARING DOSES, Outcome 5 Number of wet nights per week at followup (no SDs).

Study	Number of wet nights per week at followup (no SDs) lower dose	higher dose
20 mcg vs 40 mcg		
Miller 1990a	5.6 wet nights, n=19	5.5 wet nights, n=26
Miller 1990b	5.4 wet nights, n=19	5.7 wet nights, n=20

Comparison 4. DESMOPRESSIN: ORAL VS NOSE DROPS

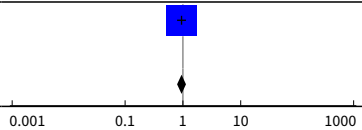
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of wet nights per week during treatment (no SDs)			Other data	No numeric data
2 Number failing to achieve 14 consecutive dry nights during treatment	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.79, 1.13]

Analysis 4.1. Comparison 4 DESMOPRESSIN: ORAL VS NOSE DROPS, Outcome 1 Number of wet nights per week during treatment (no SDs).

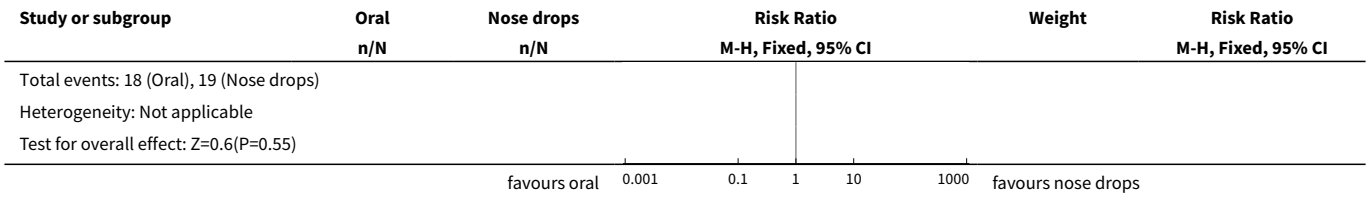
Study	Number of wet nights per week during treatment (no SDs) oral	nose drops
Fjellestad 1987#	3 wet nights, n=19	2.9 wet nights, n=19

Analysis 4.2. Comparison 4 DESMOPRESSIN: ORAL VS NOSE DROPS, Outcome 2 Number failing to achieve 14 consecutive dry nights during treatment.

Study or subgroup	Oral n/N	Nose drops n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Fjellestad 1987#	18/20	19/20		100%	0.95[0.79,1.13]
Total (95% CI)	**20**	**20**		**100%**	**0.95[0.79,1.13]**



favours oral — favours nose drops



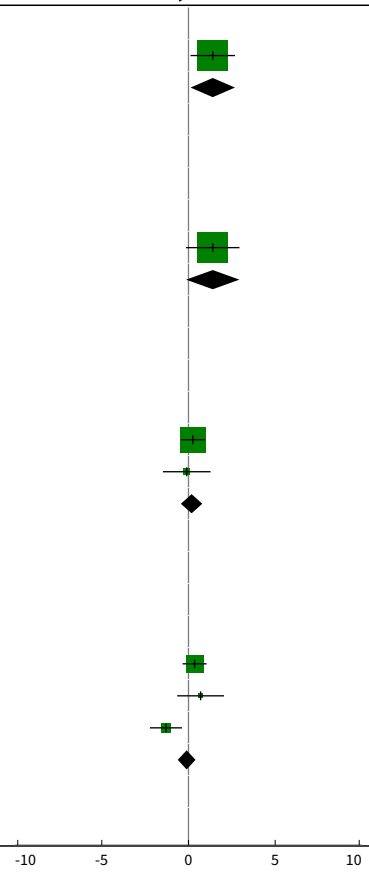
Comparison 5. DESMOPRESSIN: COMPARISON WITH OTHER DRUGS

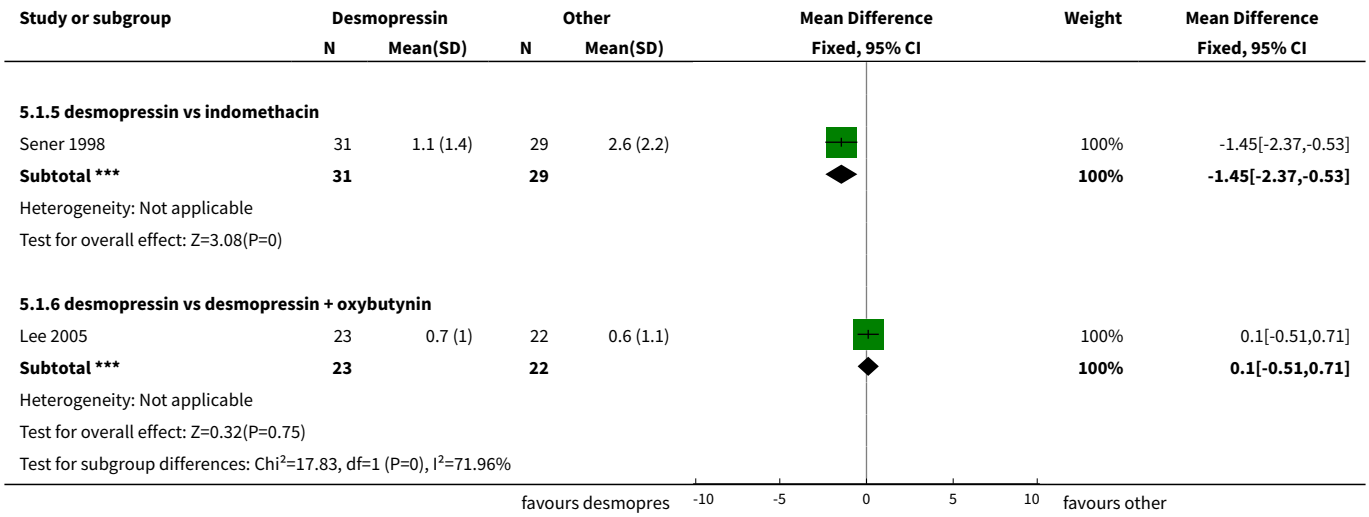
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of wet nights per week during treatment	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 desmopressin vs amitriptyline	1	31	Mean Difference (IV, Fixed, 95% CI)	1.40 [0.12, 2.68]
1.2 desmopressin vs desmopressin + amitriptyline	1	31	Mean Difference (IV, Fixed, 95% CI)	1.40 [-0.14, 2.94]
1.3 desmopressin vs imipramine (first fortnight)	2	258	Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.44, 0.80]
1.4 desmopressin vs imipramine (at end of treatment)	3	300	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.62, 0.41]
1.5 desmopressin vs indomethacin	1	60	Mean Difference (IV, Fixed, 95% CI)	-1.45 [-2.37, -0.53]
1.6 desmopressin vs desmopressin + oxybutynin	1	45	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.51, 0.71]
2 Number failing to achieve 14 consecutive dry nights during treatment	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 desmopressin vs amitriptyline	1	31	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.89, 1.61]
2.2 desmopressin vs desmopressin + amitriptyline	1	31	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.93, 1.87]
2.3 desmopressin vs diclofenac	1	62	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.30, 0.89]
2.4 desmopressin vs imipramine	2	103	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.27, 0.73]
2.5 desmopressin vs desmopressin + oxybutynin	1	45	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.51, 2.28]
3 Number of wet nights at followup	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 desmopressin vs imipramine	1	36	Mean Difference (IV, Fixed, 95% CI)	0.20 [-1.20, 1.60]
4 Number failing to achieve 14 consecutive dry nights or relapsing after cure	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 desmopressin vs amitriptyline	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 desmopressin vs desmopressin + amitriptyline	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Number of wet nights per week during treatment (no SDs)			Other data	No numeric data
5.1 desmopressin vs imipramine (first arm)			Other data	No numeric data

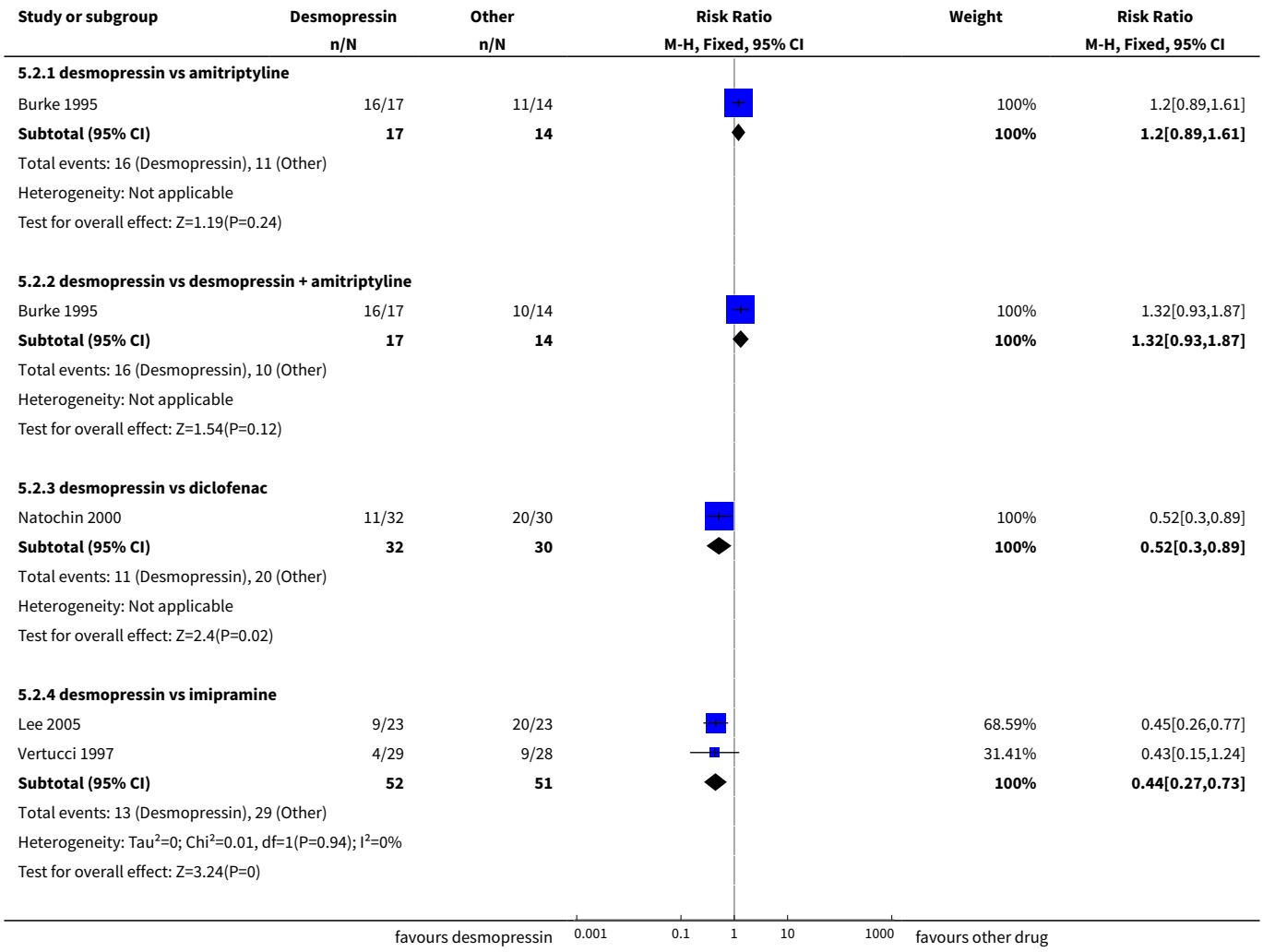
Analysis 5.1. Comparison 5 DESMOPRESSIN: COMPARISON WITH OTHER DRUGS, Outcome 1 Number of wet nights per week during treatment.

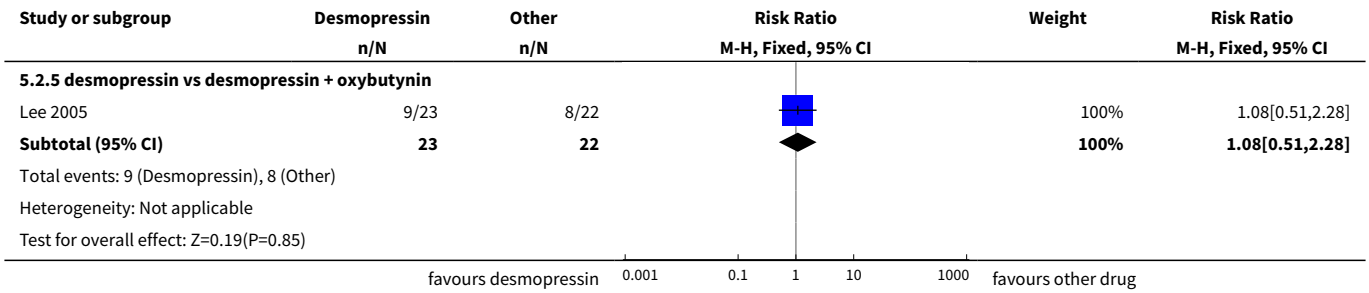
Study or subgroup	Desmopressin N	Desmopressin Mean(SD)	Other N	Other Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
5.1.1 desmopressin vs amitriptyline							
Burke 1995	17	4.7 (1.7)	14	3.3 (1.9)		100%	1.4[0.12,2.68]
Subtotal ***	**17**		**14**			**100%**	**1.4[0.12,2.68]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.14(P=0.03)							
5.1.2 desmopressin vs desmopressin + amitriptyline							
Burke 1995	17	4.7 (1.7)	14	3.3 (2.5)		100%	1.4[-0.14,2.94]
Subtotal ***	**17**		**14**			**100%**	**1.4[-0.14,2.94]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.78(P=0.07)							
5.1.3 desmopressin vs imipramine (first fortnight)							
Hoashi 1995	111	4.8 (2.6)	111	4.5 (2.6)		79.72%	0.25[-0.44,0.94]
Holt 1986	17	2.4 (2)	19	2.5 (2.2)		20.28%	-0.1[-1.47,1.27]
Subtotal ***	**128**		**130**			**100%**	**0.18[-0.44,0.8]**
Heterogeneity: Tau^2=0; Chi^2=0.2, df=1(P=0.66); I^2=0%							
Test for overall effect: Z=0.57(P=0.57)							
5.1.4 desmopressin vs imipramine (at end of treatment)							
Hoashi 1995	109	4.4 (2.6)	109	4 (2.6)		54.94%	0.35[-0.34,1.04]
Holt 1986	17	3 (2.2)	19	2.3 (1.9)		14.36%	0.7[-0.65,2.05]
Lee 2005	23	0.7 (1)	23	2 (2.1)		30.7%	-1.3[-2.22,-0.38]
Subtotal ***	**149**		**151**			**100%**	**-0.11[-0.62,0.41]**
Heterogeneity: Tau^2=0; Chi^2=9.47, df=2(P=0.01); I^2=78.88%							
Test for overall effect: Z=0.41(P=0.68)							



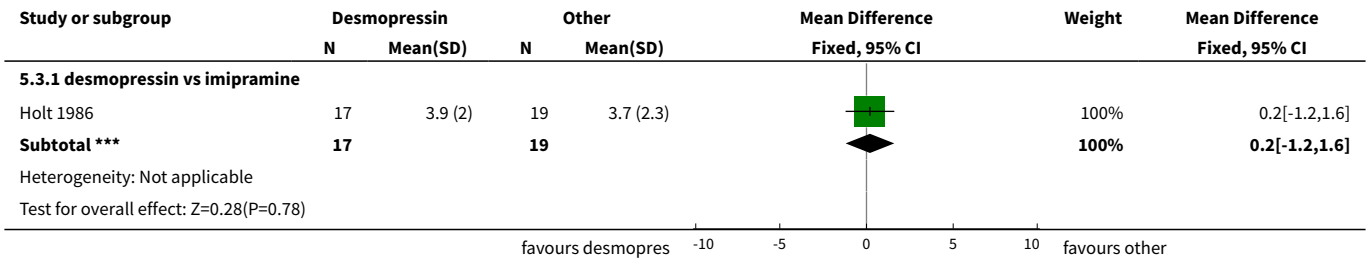


Analysis 5.2. Comparison 5 DESMOPRESSIN: COMPARISON WITH OTHER DRUGS, Outcome 2 Number failing to achieve 14 consecutive dry nights during treatment.

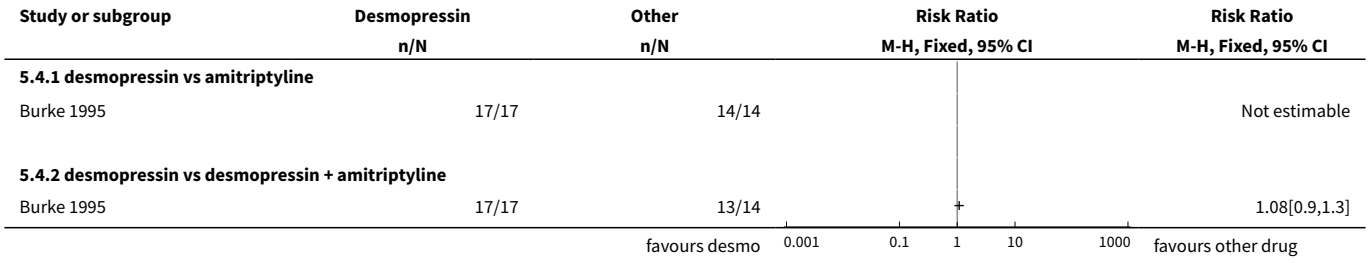




Analysis 5.3. Comparison 5 DESMOPRESSIN: COMPARISON WITH OTHER DRUGS, Outcome 3 Number of wet nights at followup.



Analysis 5.4. Comparison 5 DESMOPRESSIN: COMPARISON WITH OTHER DRUGS, Outcome 4 Number failing to achieve 14 consecutive dry nights or relapsing after cure.



Analysis 5.5. Comparison 5 DESMOPRESSIN: COMPARISON WITH OTHER DRUGS, Outcome 5 Number of wet nights per week during treatment (no SDs).

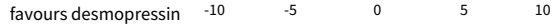
	Number of wet nights per week during treatment (no SDs)	
Study	**Desmopressin**	**Alarm**
desmopressin vs imipramine (first arm)		
Vertucci 1997	1 wet night, n=29	2.5 wet nights, n=28

Comparison 6. DESMOPRESSIN ALONE VS ALARM ALONE

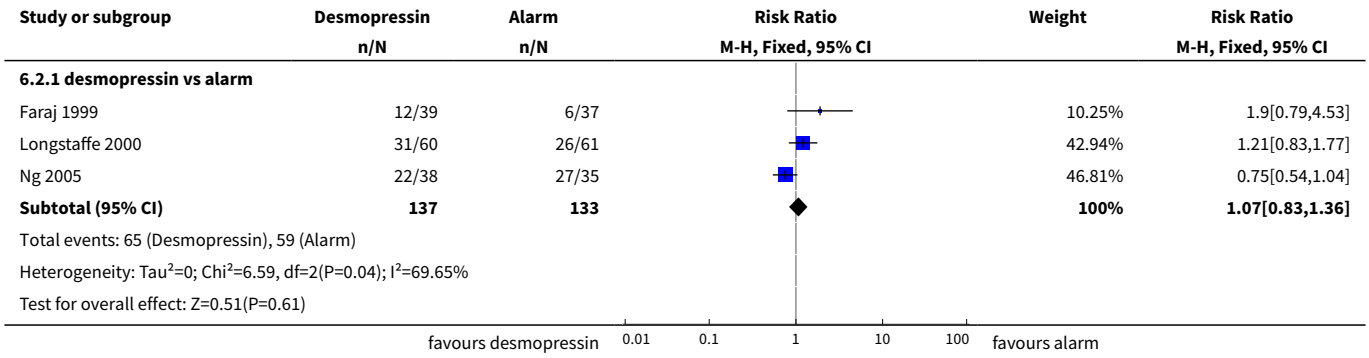
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of wet nights per week during treatment	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 desmopressin vs alarm, in first week	1	50	Mean Difference (IV, Fixed, 95% CI)	-1.70 [-2.95, -0.45]
1.2 desmopressin vs alarm, in last week	2	110	Mean Difference (IV, Fixed, 95% CI)	0.52 [-0.32, 1.36]
2 Number failing to achieve 14 consecutive dry nights during treatment	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 desmopressin vs alarm	3	270	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.83, 1.36]
3 Number failing to achieve 14 consecutive dry nights or relapsing after cure	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 desmopressin vs alarm	2	119	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [1.05, 1.91]
4 Number of wet nights per week after end of treatment	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.2 desmopressin vs alarm	1	58	Mean Difference (IV, Fixed, 95% CI)	0.90 [-0.38, 2.18]

Analysis 6.1. Comparison 6 DESMOPRESSIN ALONE VS ALARM ALONE, Outcome 1 Number of wet nights per week during treatment.

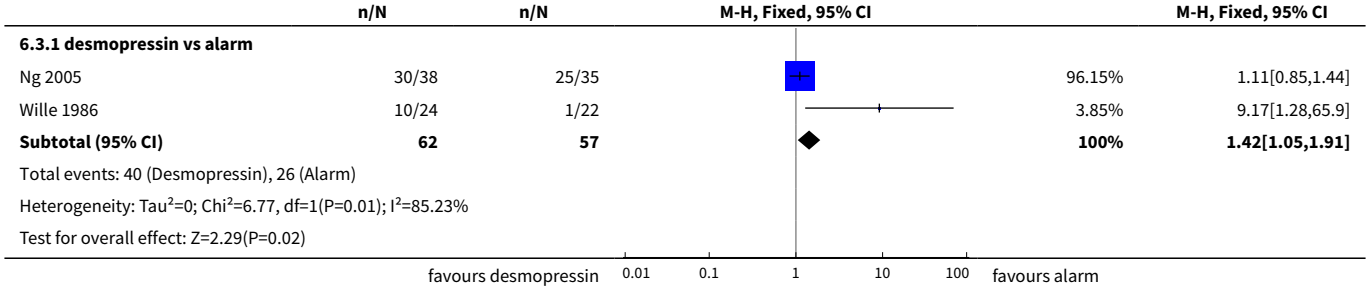
Study or subgroup	Desmopressin N	Desmopressin Mean(SD)	Alarm N	Alarm Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
6.1.1 desmopressin vs alarm, in first week							
Wille 1986	25	2.8 (2.5)	25	4.5 (2)		100%	-1.7[-2.95,-0.45]
Subtotal ***	**25**		**25**			**100%**	**-1.7[-2.95,-0.45]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.65(P=0.01)							
6.1.2 desmopressin vs alarm, in last week							
Ng 2005	36	2.6 (2.4)	28	2.8 (2.2)		55.24%	-0.2[-1.33,0.93]
Wille 1986	24	2.1 (2.5)	22	0.7 (1.9)		44.76%	1.4[0.14,2.66]
Subtotal ***	**60**		**50**			**100%**	**0.52[-0.32,1.36]**
Heterogeneity: Tau^2=0; Chi^2=3.44, df=1(P=0.06); I^2=70.95%							
Test for overall effect: Z=1.2(P=0.23)							
Test for subgroup differences: Chi^2=8.27, df=1 (P=0), I^2=87.91%							



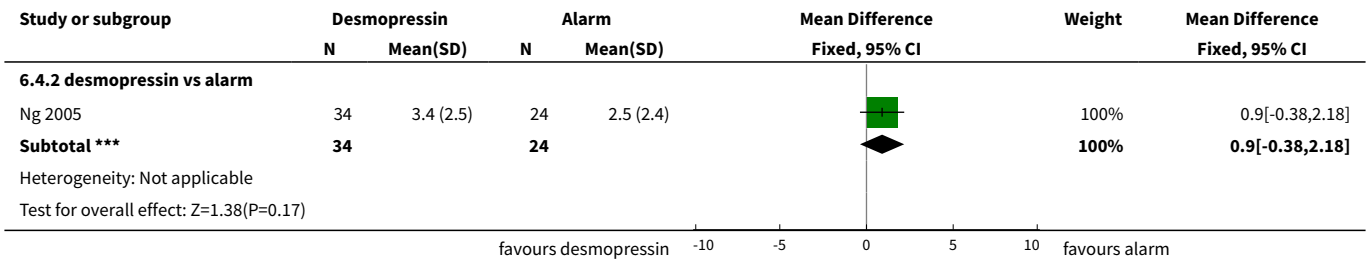
Analysis 6.2. Comparison 6 DESMOPRESSIN ALONE VS ALARM ALONE, Outcome 2 Number failing to achieve 14 consecutive dry nights during treatment.



Analysis 6.3. Comparison 6 DESMOPRESSIN ALONE VS ALARM ALONE, Outcome 3 Number failing to achieve 14 consecutive dry nights or relapsing after cure.



Analysis 6.4. Comparison 6 DESMOPRESSIN ALONE VS ALARM ALONE, Outcome 4 Number of wet nights per week after end of treatment.



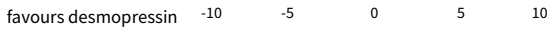
Comparison 7. DESMOPRESSIN ALONE VS DESMOPRESSIN + ALARM

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of wet nights per week during treatment	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 desmopressin alone vs desmopressin + alarm	1	65	Mean Difference (IV, Fixed, 95% CI)	1.30 [0.25, 2.35]
2 Number failing to achieve 14 consecutive dry nights during treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 desmopressin alone vs desmopressin + alarm	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.92, 2.60]
3 Number failing to achieve 14 consecutive dry nights or relapsing after cure	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 desmopressin alone vs desmopressin + alarm	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.96, 1.85]
4 Number of wet nights per week after end of treatment	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 desmopressin alone vs desmopressin + alarm	1	58	Mean Difference (IV, Fixed, 95% CI)	0.80 [-0.57, 2.17]

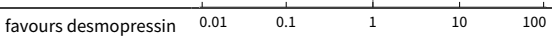
Analysis 7.1. Comparison 7 DESMOPRESSIN ALONE VS DESMOPRESSIN + ALARM, Outcome 1 Number of wet nights per week during treatment.

Study or subgroup	Desmopressin N	Desmopressin Mean(SD)	Desmo + Alarm N	Desmo + Alarm Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
7.1.1 desmopressin alone vs desmopressin + alarm							
Ng 2005	36	2.6 (2.4)	29	1.3 (1.9)		100%	1.3[0.25,2.35]
Subtotal ***	**36**		**29**			**100%**	**1.3[0.25,2.35]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=2.44(P=0.01)							

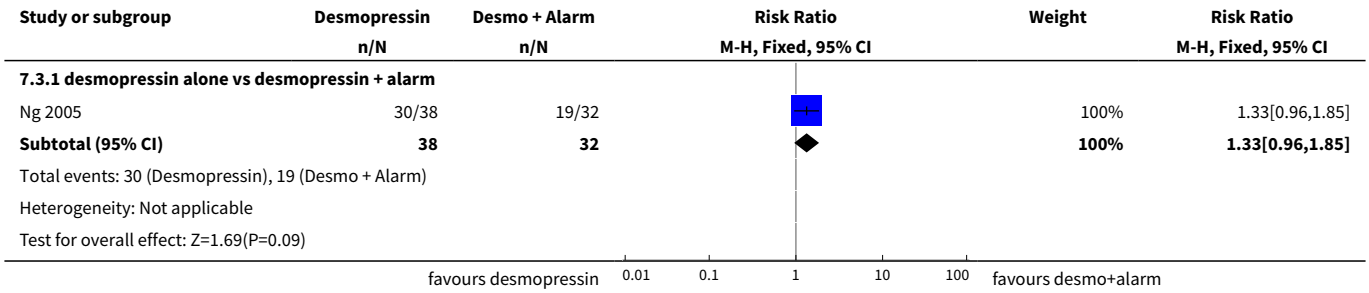


Analysis 7.2. Comparison 7 DESMOPRESSIN ALONE VS DESMOPRESSIN + ALARM, Outcome 2 Number failing to achieve 14 consecutive dry nights during treatment.

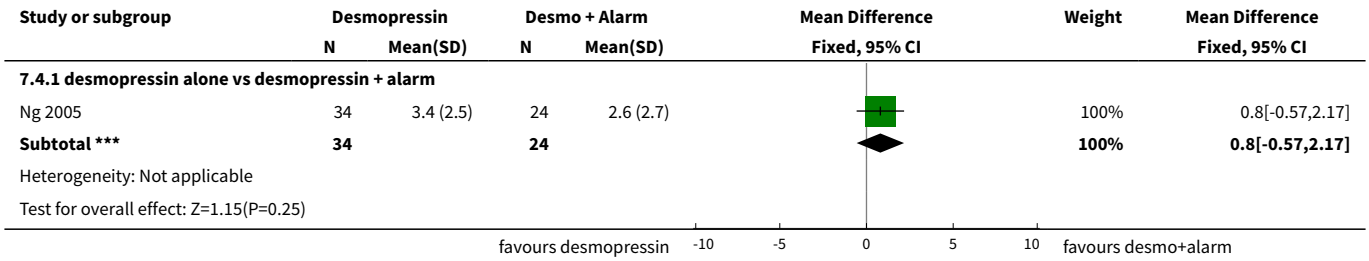
Study or subgroup	Desmopressin n/N	Desmo + Alarm n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
7.2.1 desmopressin alone vs desmopressin + alarm					
Ng 2005	22/38	12/32		100%	1.54[0.92,2.6]
Subtotal (95% CI)	**38**	**32**		**100%**	**1.54[0.92,2.6]**
Total events: 22 (Desmopressin), 12 (Desmo + Alarm)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.63(P=0.1)					



Analysis 7.3. Comparison 7 DESMOPRESSIN ALONE VS DESMOPRESSIN + ALARM, Outcome 3 Number failing to achieve 14 consecutive dry nights or relapsing after cure.



Analysis 7.4. Comparison 7 DESMOPRESSIN ALONE VS DESMOPRESSIN + ALARM, Outcome 4 Number of wet nights per week after end of treatment.

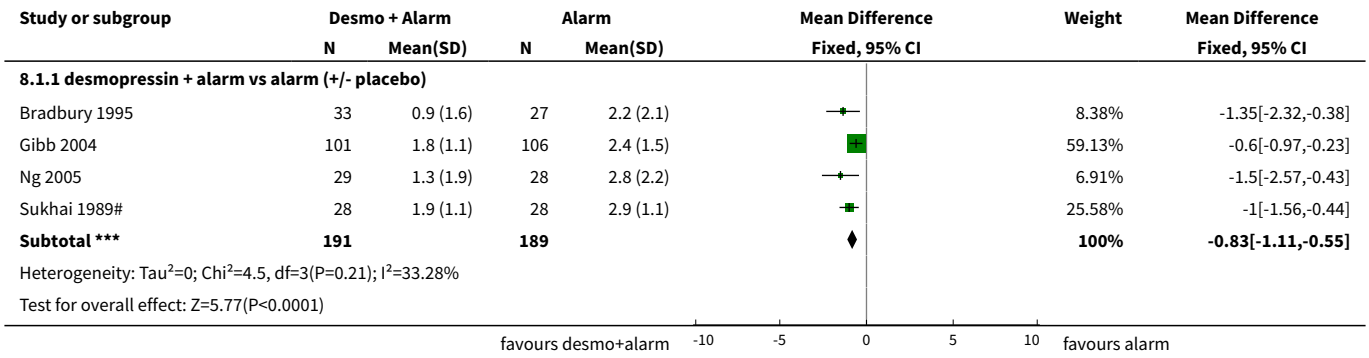


Comparison 8. DESMOPRESSIN + ALARM VS ALARM ALONE

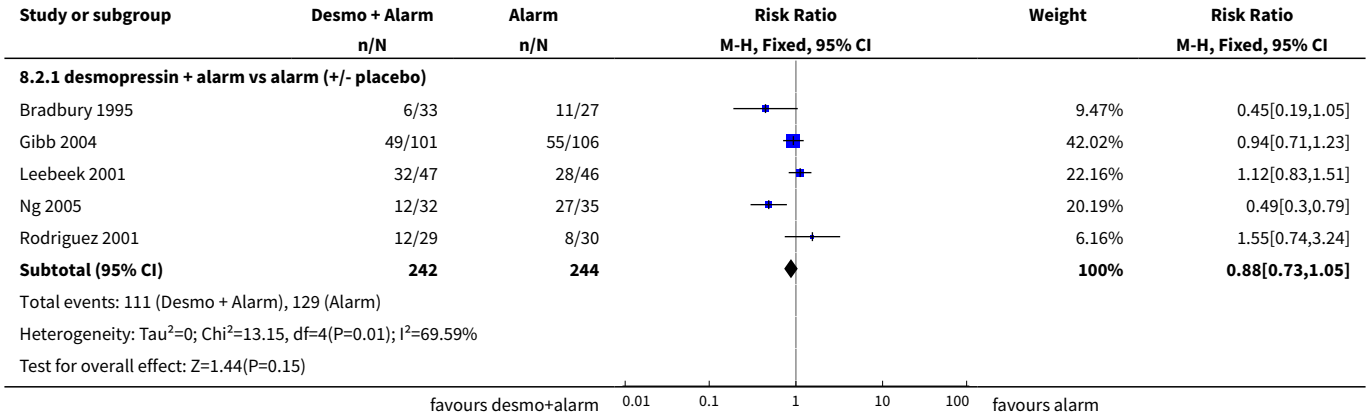
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of wet nights per week during treatment	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 desmopressin + alarm vs alarm (+/- placebo)	4	380	Mean Difference (IV, Fixed, 95% CI)	-0.83 [-1.11, -0.55]
2 Number failing to achieve 14 consecutive dry nights during treatment	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 desmopressin + alarm vs alarm (+/- placebo)	5	486	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.73, 1.05]
3 Number failing to achieve 14 consecutive dry nights or relapsing after cure	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 desmopressin + alarm vs alarm (+/- placebo)	4	427	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.76, 1.08]
4 Number of wet nights per week after end of treatment	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 desmopressin + alarm vs alarm alone	1	48	Mean Difference (IV, Fixed, 95% CI)	0.10 [-1.35, 1.55]
5 Number of wet nights per week during treatment (no SDs)			Other data	No numeric data
5.1 desmopressin + alarm vs alarm (+/- placebo)			Other data	No numeric data
6 Number of wet nights per week after treatment stops (no SDs)			Other data	No numeric data
6.1 desmopressin + alarm vs alarm (+/- placebo)			Other data	No numeric data

Analysis 8.1. Comparison 8 DESMOPRESSIN + ALARM VS ALARM ALONE, Outcome 1 Number of wet nights per week during treatment.

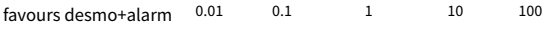


Analysis 8.2. Comparison 8 DESMOPRESSIN + ALARM VS ALARM ALONE, Outcome 2 Number failing to achieve 14 consecutive dry nights during treatment.



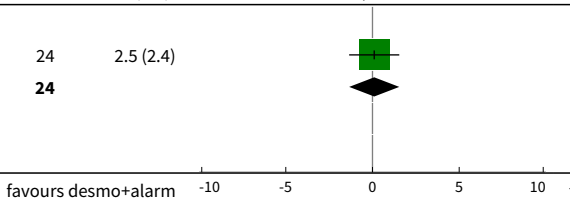
Analysis 8.3. Comparison 8 DESMOPRESSIN + ALARM VS ALARM ALONE, Outcome 3 Number failing to achieve 14 consecutive dry nights or relapsing after cure.

Study or subgroup	Desmo + Alarm n/N	Alarm n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
8.3.1 desmopressin + alarm vs alarm (+/- placebo)					
Bradbury 1995	10/33	14/27		13.15%	0.58[0.31,1.1]
Gibb 2004	56/101	58/106		48.33%	1.01[0.79,1.3]
Leebeek 2001	20/47	21/46		18.13%	0.93[0.59,1.47]
Ng 2005	19/32	25/35		20.39%	0.83[0.58,1.19]
Subtotal (95% CI)	**213**	**214**		**100%**	**0.91[0.76,1.08]**
Total events: 105 (Desmo + Alarm), 118 (Alarm)					
Heterogeneity: Tau²=0; Chi²=2.88, df=3(P=0.41); I²=0%					
Test for overall effect: Z=1.09(P=0.28)					



Analysis 8.4. Comparison 8 DESMOPRESSIN + ALARM VS ALARM ALONE, Outcome 4 Number of wet nights per week after end of treatment.

Study or subgroup	Desmo + Alarm N	Mean(SD)	Alarm N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
8.4.1 desmopressin + alarm vs alarm alone							
Ng 2005	24	2.6 (2.7)	24	2.5 (2.4)		100%	0.1[-1.35,1.55]
Subtotal ***	**24**		**24**			**100%**	**0.1[-1.35,1.55]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.14(P=0.89)							



Analysis 8.5. Comparison 8 DESMOPRESSIN + ALARM VS ALARM ALONE, Outcome 5 Number of wet nights per week during treatment (no SDs).

Study	Number of wet nights per week during treatment (no SDs) Desmopressin + Alarm	Alarm alone
desmopressin + alarm vs alarm (+/- placebo)		
Leebeek 2001	2.93 wet nights, n=47	3.86 wet nights, n=45

Analysis 8.6. Comparison 8 DESMOPRESSIN + ALARM VS ALARM ALONE, Outcome 6 Number of wet nights per week after treatment stops (no SDs).

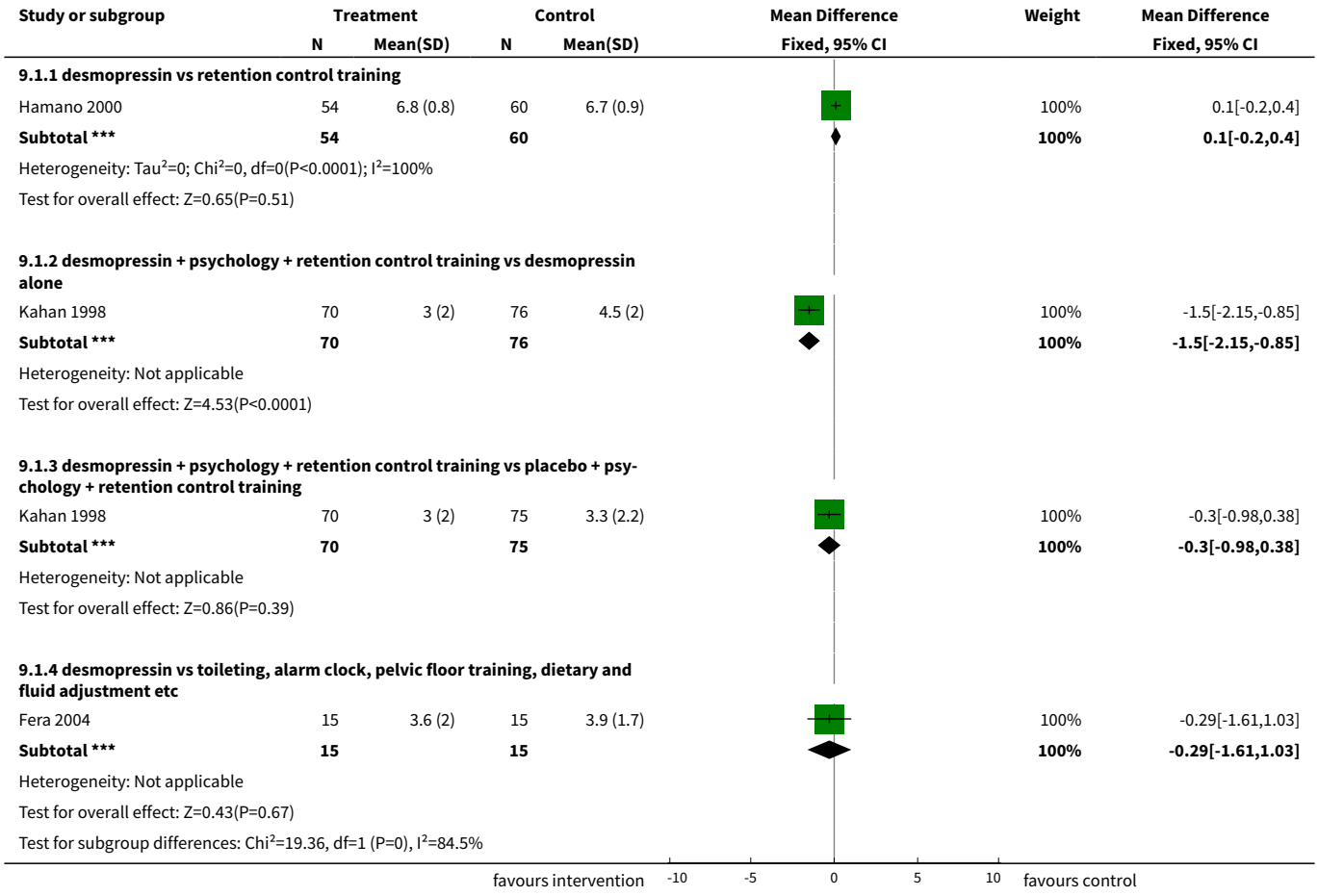
Study	Number of wet nights per week after treatment stops (no SDs) Desmopressin + Alarm	Alarm alone
desmopressin + alarm vs alarm (+/- placebo)		
Leebeek 2001	2.72 wet nights, n=41	1.90 wet nights, n=37

Comparison 9. DESMOPRESSIN VS BEHAVIOURAL METHODS

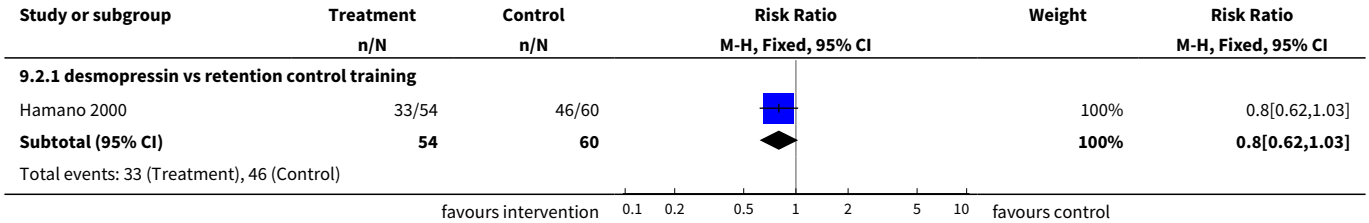
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of wet nights per week during treatment	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 desmopressin vs retention control training	1	114	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.20, 0.40]
1.2 desmopressin + psychology + retention control training vs desmopressin alone	1	146	Mean Difference (IV, Fixed, 95% CI)	-1.5 [-2.15, -0.85]
1.3 desmopressin + psychology + retention control training vs placebo + psychology + retention control training	1	145	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.98, 0.38]
1.4 desmopressin vs toileting, alarm clock, pelvic floor training, dietary and fluid adjustment etc	1	30	Mean Difference (IV, Fixed, 95% CI)	-0.29 [-1.61, 1.03]
2 Number failing to achieve 14 consecutive dry nights during treatment	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 desmopressin vs retention control training	1	114	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.62, 1.03]
2.2 desmopressin + psychology + retention control training vs desmopressin alone	1	146	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.91, 1.48]
2.3 desmopressin + psychology + retention control training vs placebo + psychology + retention control training	1	145	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.68, 0.98]
2.4 desmopressin vs toileting, alarm clock, pelvic floor training, dietary and fluid adjustment etc	1	30	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.66, 37.85]
3 Number of wet nights per week at followup	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.2 desmopressin + psychology + retention control training vs desmopressin alone	1	146	Mean Difference (IV, Fixed, 95% CI)	-2.1 [-2.67, -1.53]
3.3 desmopressin + psychology + retention control training vs placebo + psychology + retention control training	1	144	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.01, 0.21]
4 Number failing to achieve 14 consecutive dry nights or relapsing after cure	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 desmopressin vs retention control training	1	114	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.96, 1.24]
4.2 desmopressin + psychology + retention control training vs desmopressin alone	1	146	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.91, 1.06]

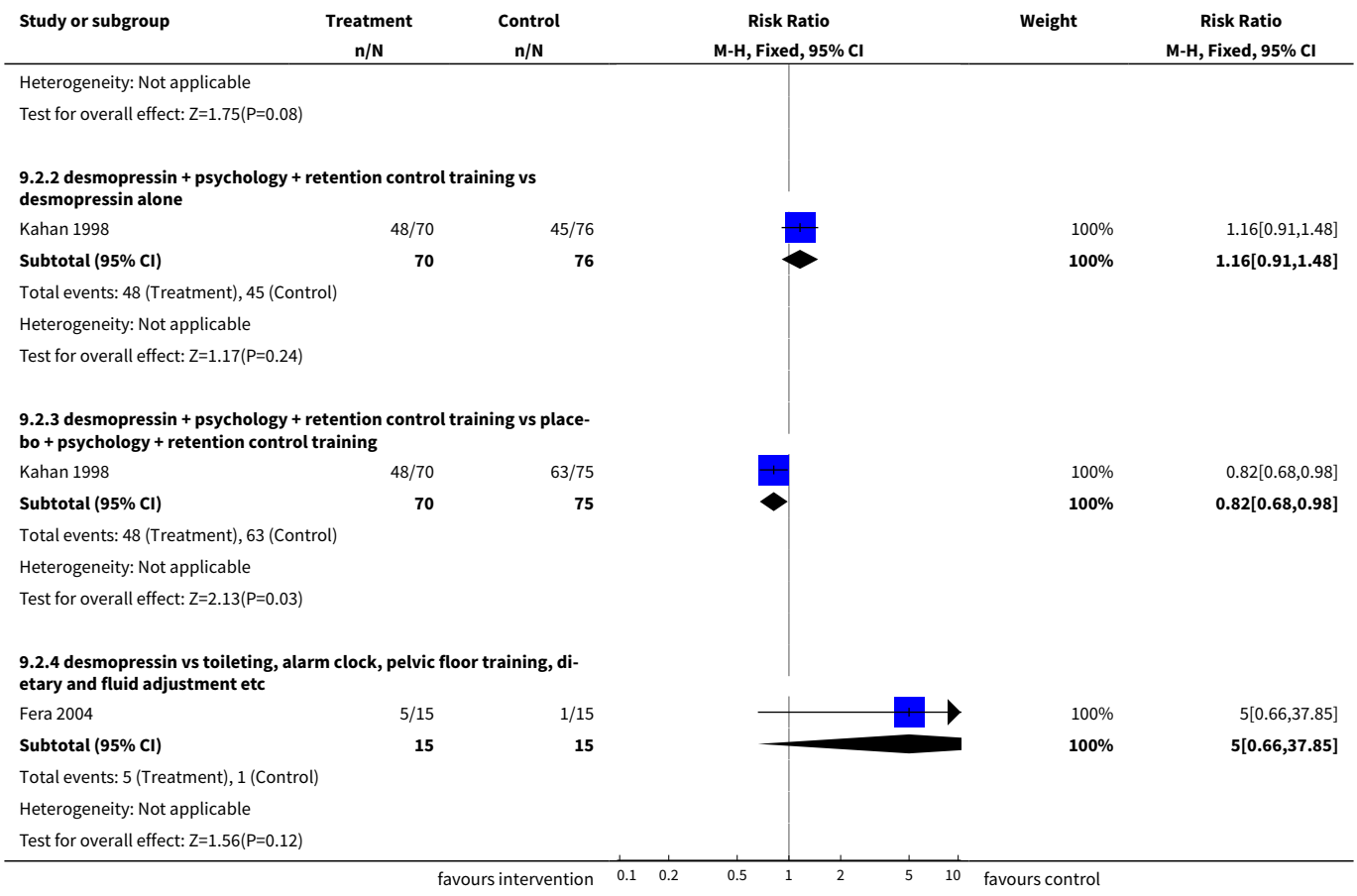
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3 desmopressin + psychology + retention control training vs placebo + psychology + retention control training	1	145	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.94, 1.12]

Analysis 9.1. Comparison 9 DESMOPRESSIN VS BEHAVIOURAL METHODS, Outcome 1 Number of wet nights per week during treatment.

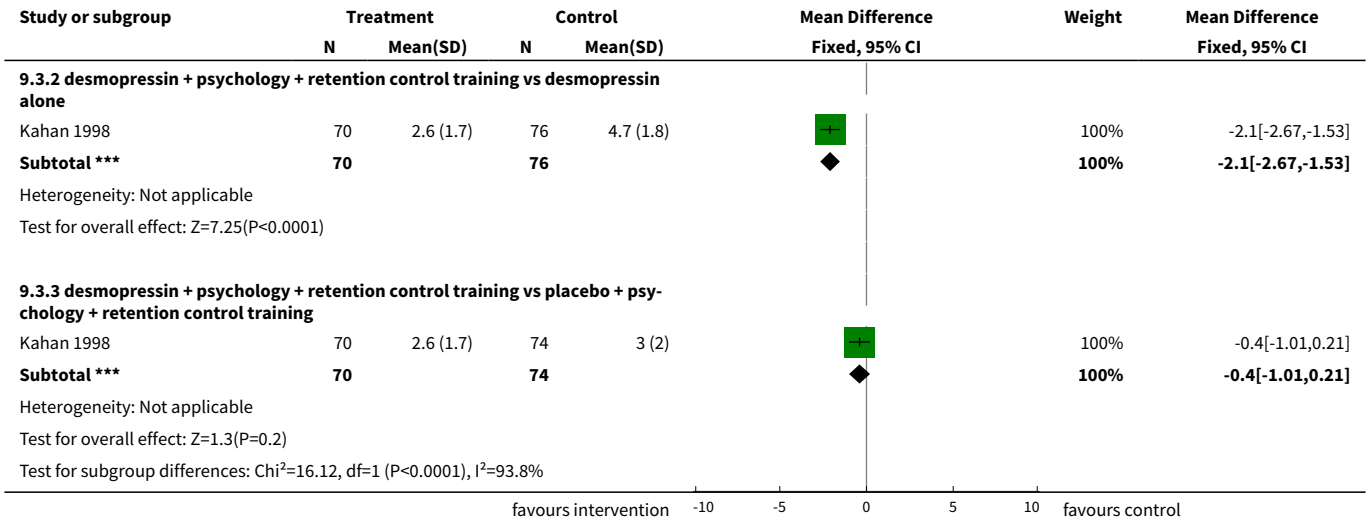


Analysis 9.2. Comparison 9 DESMOPRESSIN VS BEHAVIOURAL METHODS, Outcome 2 Number failing to achieve 14 consecutive dry nights during treatment.

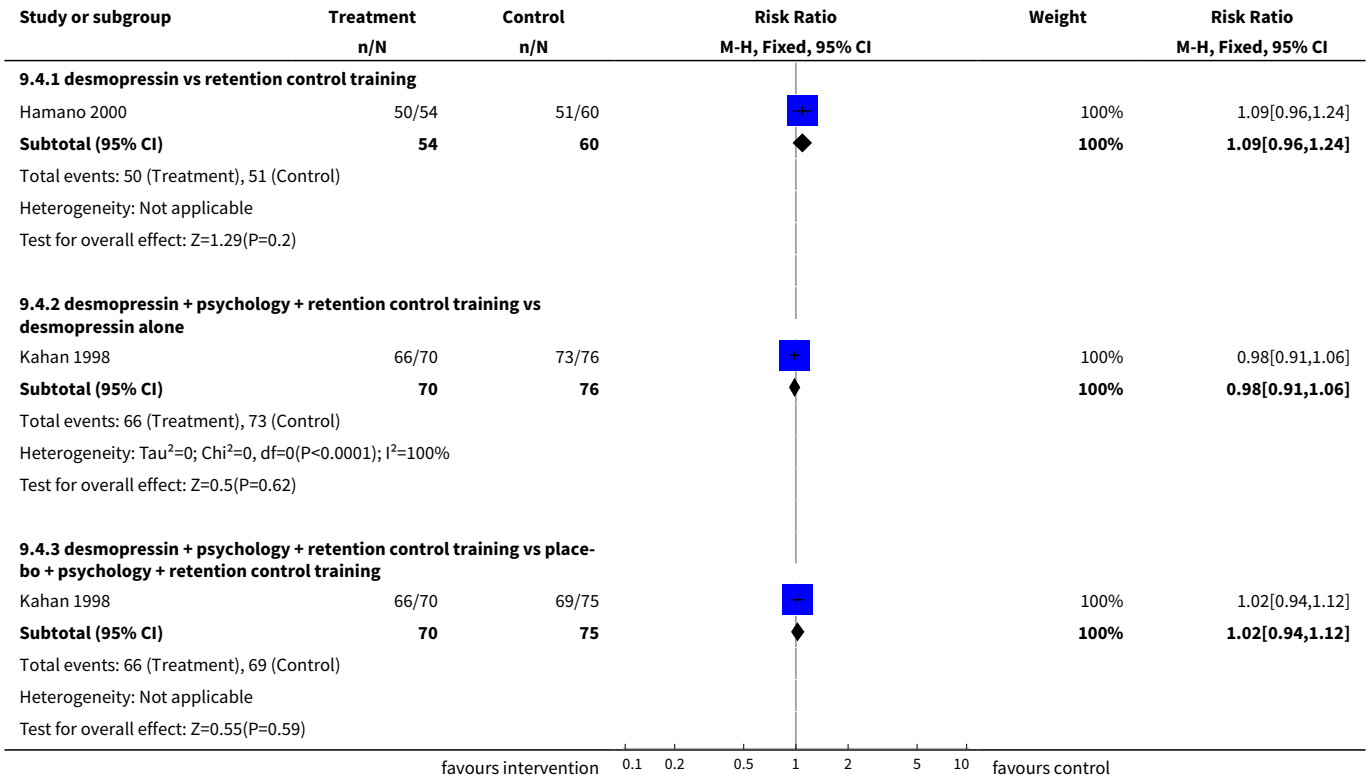




Analysis 9.3. Comparison 9 DESMOPRESSIN VS BEHAVIOURAL METHODS, Outcome 3 Number of wet nights per week at followup.



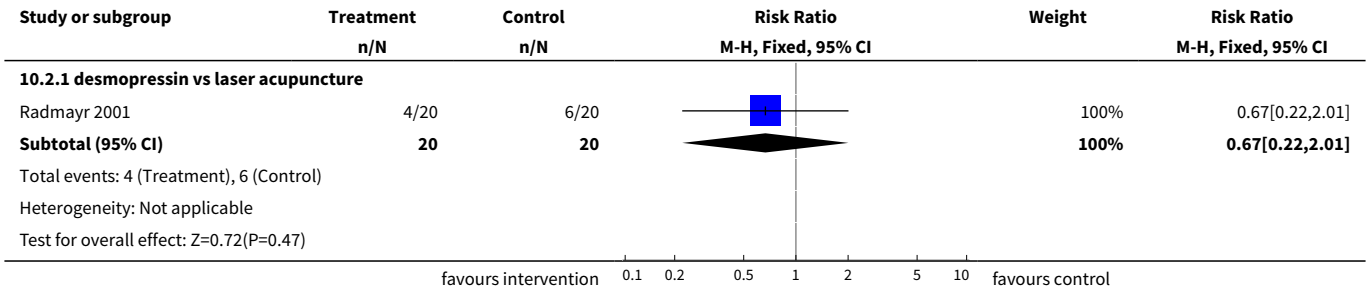
Analysis 9.4. Comparison 9 DESMOPRESSIN VS BEHAVIOURAL METHODS, Outcome 4 Number failing to achieve 14 consecutive dry nights or relapsing after cure.



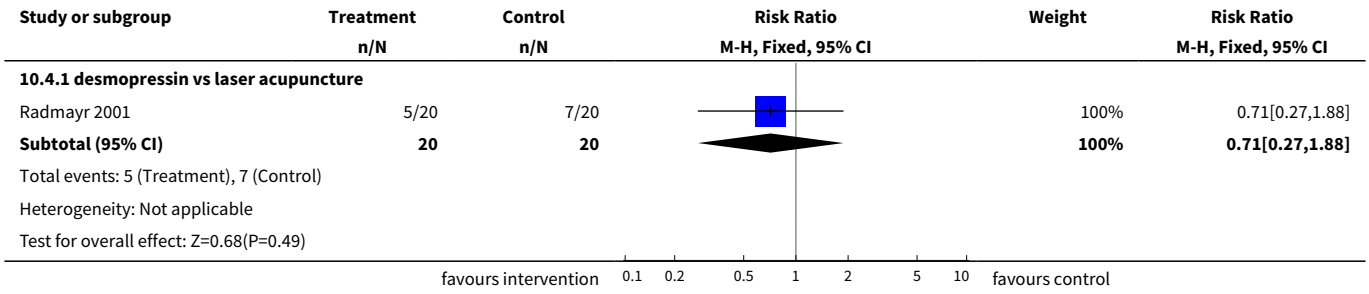
Comparison 10. DESMOPRESSIN VS COMPLEMENTARY METHODS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Number failing to achieve 14 consecutive dry nights during treatment	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 desmopressin vs laser acupuncture	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.22, 2.01]
4 Number failing to achieve 14 consecutive dry nights or relapsing after cure	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 desmopressin vs laser acupuncture	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.27, 1.88]

Analysis 10.2. Comparison 10 DESMOPRESSIN VS COMPLEMENTARY METHODS, Outcome 2 Number failing to achieve 14 consecutive dry nights during treatment.



Analysis 10.4. Comparison 10 DESMOPRESSIN VS COMPLEMENTARY METHODS, Outcome 4 Number failing to achieve 14 consecutive dry nights or relapsing after cure.



WHAT'S NEW

Date	Event	Description
16 September 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 2000
Review first published: Issue 2, 2000

Date	Event	Description
4 October 2006	New search has been performed	Minor update Issue 3 2006. Includes 5 new trials, and the previous tentative conclusions regarding alarms were strengthened: there is now firmer evidence that alarms are more effective (lower relapse rates) than desmopressin after treatment stops. There is no statistically significant evidence to suggest that combining desmopressin and alarm treatment is more effective than alarm treatment alone. Desmopressin appeared to be better than imipramine during treatment.

Date	Event	Description
20 May 2004	New search has been performed	Minor update Issue 3, 2004. Six new studies were excluded and one new trial (Gibb 2004) was included. The conclusions were, however, unchanged.
21 May 2002	New citation required and conclusions have changed	Substantive amendment. The review was updated for Issue 3, 2002. 18 new trials were added, and the data from some old trials recalculated to include relapse rates and failure rates together.

CONTRIBUTIONS OF AUTHORS

CMAG (the contact reviewer) originally based this review on work done at the NHS Centre for Reviews and Dissemination, University of York, UK (see acknowledgements). CMAG used the data extracted by the York reviewers, converted them into Cochrane Review format, and separated them into seven component intervention reviews (of which this is one). This review includes trials from the York review plus extra ones identified since then. JHCE performed double data abstraction for the new trials, edited the text and provided a clinical perspective and interpretation.

DECLARATIONS OF INTEREST

JHCE has received reimbursement for attending a conference, fees for lecturing and a consultancy fee which was paid into a research fund from Ferring Pharmaceuticals, manufacturers of desmopressin.

SOURCES OF SUPPORT

Internal sources

- Chief Scientist Office, Sottish Executive Health Department, UK.

External sources

- National Health Service Research and Development Programme, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Deamino Arginine Vasopressin [*therapeutic use]; Enuresis [*drug therapy]; Randomized Controlled Trials as Topic; Renal Agents [*therapeutic use]

MeSH check words

Child; Humans